



## The effects of add-on therapy of *Phyllanthus Emblica* (Amla) on laboratory confirmed COVID-19 Cases: A randomized, double-blind, controlled trial

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### ABSTRACT

**Objective:** This randomized, double-blind, controlled trial (RCT) aimed to evaluate the effect of *Phyllanthus Emblica* (Amla) as an add-on therapy on COVID-19 related biomarkers and clinical outcomes in COVID-19 patients.

**Methods:** In this RCT, sixty-one patients were randomly assigned into two arms [the intervention (n=31) and control arms (n=30)]. The effect of Amla on diagnostic Reverse-transcription Polymerase Chain Reaction (RT-PCR) test results between the first and the last days of the study, the length of stay (LOS) in hospital, the percentage of lung involvement on CT scans, changes in the clinical symptoms, and the laboratory markers were assessed.

**Results:** The two study groups had similar baseline demographics and characteristics in terms of medical history. The mean of LOS in the intervention arm (4.44 days) was significantly shorter than in the control arm (7.18 days,  $P < 0.001$ ); RT-PCR results were not significantly different between the two arms ( $P = 0.07$ ). All clinical variables decreased over time in the two groups ( $P < 0.001$ ). However, the difference between the two groups in terms of fever ( $P = 0.004$ ), severity of cough ( $P = 0.001$ ), shortness of breath ( $P = 0.004$ ), and myalgia ( $P = 0.005$ ) were significant, but this intergroup comparison was not significant with regard to respiratory rate ( $P = 0.29$ ), severity of chills ( $P = 0.06$ ), sore throat ( $P = 0.22$ ), and weakness ( $P = 0.12$ ). Out of the eight evaluated para-clinical variables, three variables showed significant improvement in the intervention arm, including the mean increase in oxygen saturation (SpO<sub>2</sub>) level ( $P < 0.001$ ), the reduction in the mean percentage of lung involvement on CT ( $P < 0.001$ ), and the improvement in C-reactive protein test results ( $P < 0.001$ ).

**Conclusion:** Organic herbal Amla tea cannot significantly affect the RT-PCR results and or degree of lung involvement. Nevertheless, it showed an ameliorative effect on the severity of clinical signs and CRP levels. Also, Amla tea may shorten the recovery times of symptoms and LOS in COVID-19 patients.

### 1. Introduction

The progression of the coronavirus (COVID-19) pandemic caused numerous difficulties for people worldwide. Although some eligible treatment options identified against COVID-19 such as immunotherapies [], there is still a strong desire to utilize herbal medicines,

especially in the Middle East. Therefore, scientific evaluation of the efficacy of herbal medicines and their possible side effects can provide a more precise strategy for the administration of this class of drugs. Although some of the therapeutic options have shown partially good effects on COVID-19 patients' recovery, there are a number of side effects related to these treatments, such as bradycardia in critical patients

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following Lopinavir-Ritonavir,<sup>1</sup> and breathing problems following extended Remdesivir consumption.<sup>2</sup>

Prevention and treatment are well-known strategies in both traditional Persian medicine and Chinese medicine. In addition to their therapeutic effect, the issue of cost-effectiveness is also a potential benefit of these disease management practices.<sup>3</sup> One of these medicinal plants in traditional medicine is called *Emblica Officinalis Gaertn* or *Phyllanthus Emblica Linn. (Euphorbeaceae)*, popularly referred to as Indian gooseberry or Amla. Due to the special medicinal and pharmaceutical properties, each part of this plant has fruitful anti-inflammatory, nootropic, antioxidant, anticancer, adaptogenic, anti-diabetic, antimicrobial, antiviral, as well as immunomodulatory effects besides preserving the vitality of the human cells.<sup>4-7</sup>

Because of the pandemic spread of the SARS-CoV-2 infection and the morbidity and mortality associated with COVID-19 and its threat to human health and economies worldwide, finding an effective and affordable treatment is crucial<sup>8</sup>. Therefore, we aimed to evaluate the effects of *Phyllanthus Emblica* (Amla) as an add-on therapy on laboratory-confirmed admitted COVID-19 patients using a randomized, double-blind, controlled trial (RCT).

### 1.1. Objective and hypothesis

The present study was conducted to determine the effects of Amla on diagnostic RT-PCR test results in patients with COVID-19 between the first and last days of the study (day 10), the length of stay (LOS) in hospital, the symptoms and signs of patients with COVID-19, including, chills, cough, shortness of breath, weakness, sore throat, respiratory rate, myalgia and fever, the laboratory results of patients with COVID-19 between the first and last days of the study including the mean number of lymphocytes, the mean hemoglobin (Hb) level, the polymorphonuclear (PMN) count, the mean number of platelets (PLT), the mean erythrocyte sedimentation rate (ESR) level, the C reactive protein (CRP) level and final RT-PCR result, oxygen saturation (SpO<sub>2</sub>), as well as the mean percentage of lung involvement on computed tomography (CT) scans of patients with COVID-19 between the first and last days of the study.

The three hypotheses of this study included observing significant differences in the results of RT-PCR, daily recorded signs and symptoms and paraclinical results in the intervention arm compared to the control arm. The null hypothesis included the rejection of the aforementioned hypotheses.

## 2. Methods

### 2.1. Study design

This clinical trial was conducted from May 1<sup>st</sup>, 2020 to June 1<sup>st</sup>, 2020 at Razi and Sina Hospitals, affiliated with Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran. In this RCT, 61 patients were randomly assigned into two arms, i.e., the intervention (n=31) and the control arms (n=30). The effects of Amla on the clinical and paraclinical symptoms were assessed, including the diagnostic Reverse-transcription Polymerase Chain Reaction (RT-PCR) test results on the first and last days of the study (day 10), the length of hospital stay (LOS), the percentage of lung involvement on CT, as well as the laboratory markers.

### 2.2. Participants

Study inclusion criteria were age over 18 years, a positive RT-PCR test for COVID-19, pulmonary involvement on chest imaging, hospitalization with the following criteria: fever ( $\geq 38^{\circ}\text{C}$  based on oral or axillary measurements) or respiratory rate above 24 per minute and cough within 8 days of disease onset. The exclusion criteria were disapproval by physicians or any condition that did not allow the protocol to be

followed safely, severe liver disease, advanced kidney disease, an allergic reaction to the Amla, pregnancy or breastfeeding, transfer to another non-targeted hospital within the next 72 hours, being administered any experimental treatment for COVID-19 in the 30 day-period prior to evaluation and a history of taking angiotensin-converting enzyme inhibitors; also, patients with a WHO severity score  $> 6$  were excluded from the study.<sup>9</sup>

### 2.3. Intervention protocols

All eligible patients enrolled in this study had voluntarily signed the written informed consent forms. None of the participants were deprived of their routine treatments for COVID-19 during the trial. Patients had the choice to leave the study freely at any time without disruption of their routine treatment.

After diagnosing COVID-19, an infectious disease specialist prescribed 200 mg hydroxychloroquine sulfate tablets along with Lopinavir/ritonavir (Kaletra) tablets (every 12 hours, two tablets after meals for 7 to 14 days) as the first-line therapy for all patients. In the intervention arm, patients received 2 grams of the sachet powder of Amla or 100 cc Amla tea per day for 10 days in addition to routine COVID-19 treatments. In the control arm, patients received a placebo along with routine treatment for COVID-19. The placebo was 2 g of sachet powder of Starch for oral solution. At the beginning of the intervention, precise instructions and "dos and don'ts" were explained to all patients in detail.

### 2.4. Sachet powder preparation method and interventions

The fruits of the dried Amla plant had been purchased from a valid pharmaceutical plant store in April 2020. This plant had been identified by an herbalist (Dr. Amir Siahpoosh, Associate Professor of Pharmacognosy, AJUMS, Ahvaz, Iran) with extensive knowledge about this particular plant. The samples of this plant were identified and kept in the herbarium of the Department of Pharmacognosy, AJUMS, Ahvaz, Iran (herbarium code: A2023401010FP). The Sachet powder of placebo and Amla were prepared in the School of Pharmacy, AJUMS. Total polyphenolic contents of *Phyllanthus Emblica* was equivalent to 39.56 gram gallic acid per 100 g extract according to the Folin Ciocalteu method. The placebo was prepared using the Pharmacopoeia formula for sachet powder in a standard color and flavor similar to the Amla powder; their taste and color were evaluated qualitatively by a group of volunteers who confirmed their resemblance. Two similar sachets were eventually prepared and kept in storage. Each participant in the intervention arm received 2 g of sachet powder every day (Amla every 12 hours), while the controls received 2 g of sachet powder of placebo every 12 hours. The nurses in charge were advised to provide a dose of the powder overnight 1-1.5 hours before bedtime followed by another dose twelve hours later. Given the potential drug-food interactions, patients were also warned to avoid taking the medicine with food. Both types of sachet powder were identical in terms of cover and taste and were prepared by a person who was not involved in the clinical trial.

The sachet powders were distributed among the nurses in charge for each case, and they were asked to administer medication for 10 days. Furthermore, all of them were asked to contact the investigation team in case of any side effects or drug poisoning. Also, we tracked them by phone on a daily basis to inquire about any probable problems. We explained to the nurses that the participants who had left at least 20% of the sachet powders after 10 days would be considered as non-compliant and excluded from the study; however, COVID-19 treatment would be continued for them.

### 2.5. Outcomes

The primary outcome was a change in the COVID-19 diagnostic test results between the first and last days of the study using RT-PCR. Secondary outcomes included changes in the LOS, clinical symptoms [e.g.,

daily body temperature, respiratory rate, chills, cough, sore throat, myalgia, weakness and shortness of breath], and laboratory results between the first and last days of the study, including peripheral blood lymphocytes, CRP levels, blood hemoglobin (Hb) levels, mean PMN cell counts, PLT counts, ESR levels, SpO<sub>2</sub>; also, the pulmonary imaging results between the first and last day of the study, i.e., chest radiographs and CT scans, were assessed as secondary outcomes.

2.6. Sample Size

Due to the lack of data on possible effects of this new treatment, and having no hypothesis regarding it, this study was an explorative and or pilot study consisting of a minimum number of 30 COVID-19 cases in each group.

2.7. Randomization, blinding, and allocation concealment

The allocation of patients to each treatment arm was done by the block randomization method. The randomization unit was the individual; the randomization sequence was created using WinPEPI program (version 11.43), and was stratified by center with a 1:1 allocation ratio using a random block size of 6, and allocation concealment was done by assigning unicode.

In this parallel-group, double-blind, placebo-controlled RCT, the drugs for both groups were in the same aluminum containers, and the Amla plant did not have a specific odor and its color and taste were

similar to the placebo. The sachet powders were placed into a matte envelope and an unique code assigned by [www.sealedenvelope.com](http://www.sealedenvelope.com) was pasted on every envelope. The list of numbers was given to a statistical consultant for subsequent data analysis. All patients, physicians and investigators were blind to the kind of drugs and nurses were responsible for prescribing medication to patients.

2.8. Statistical analysis

In this study, the continuous variables were reported as mean with standard deviation and the comparisons between groups and within groups were performed by the independent sample t-test and paired sample t-test, respectively. Categorical variables were presented as numbers and percentages and the comparisons between groups were performed by chi-square and/or Fisher exact test. The comparisons for continuous clinical variables and ordinal variables of intragroup and intergroup during time (intervention and control group) were performed using the repeated measures ANOVA test and Generalized Estimating Equations (GEE), respectively. Plots were created by Graphpad prism 8. The data were analyzed using the statistical package for social science (SPSS Inc., Chicago, version 26) and p-value < 0.05 was considered statistically significant.

2.9. Ethical considerations

This clinical trial was approved by the Ethics Committee of AJUMS

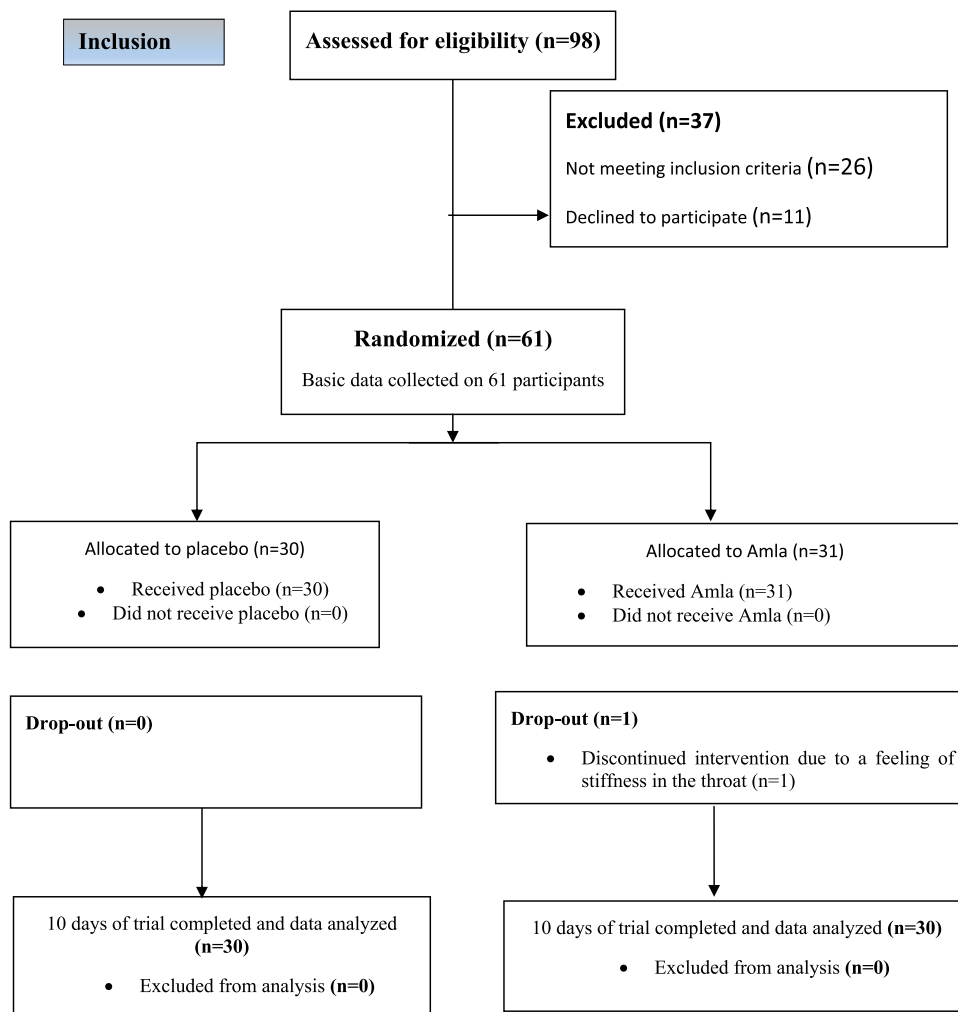


Fig. 1. The flowchart of the Distribution of Participants with Coronavirus disease 2019 (COVID-19) During the Study.

(Code: IR.AJUMS.REC.1399.011) and registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20200404046937N2).

### 3. Results

#### 3.1. Demographic information

Sixty-one patients with laboratory confirmed COVID-19 were assigned to this RCT and were randomly divided to two arms, i.e. an intervention arm (n= 31) and a control arm (n=30). One patient left the intervention arm due to a feeling of stiffness in the throat. Finally, 30 subjects were analyzed in each study arm. Fig. 1 shows the CONSORT flow diagram associated with subjects. The patients' mean (SD) age in the intervention and control groups were 47.87±14.31 and 44.27±11.20 years, respectively, without any statistically significant difference (P:0.28). Moreover, there was no significant difference between the groups in terms of height, weight, body mass index (BMI), gender, marital status, education level, occupation, living setting, history of pulmonary infectious disease, treatment history, history of type of treatment and comorbidities (P>0.05), as shown in Table 1. Therefore, the two arms of the study had similar baseline characteristics.

#### 3.2. Patients' primary outcomes

At the beginning of the study, all participants had positive RT-PCR results for COVID-19, and at the end, there was no significant difference between the two arms (P = 0.07).

**Table 1**  
Demographic characteristics of admitted COVID-19 patients as well as baseline medical history data in both arms of study.

variables	InterventionN=30	ControlN=30	P-Value
Age, Y	47.87±14.31	44.27±11.20	0.28
Height, cm <sup>2</sup>	168.27±6.44	169.90±7.75	0.38
Weight, Kg	77.30±12.38	74.80±12.81	0.44
BMI, Kg/m <sup>2</sup>	27.22±3.40	25.77±3.05	0.08
<b>Gender</b>			
Male	12[40]	17(56.7)	0.19
Female	18[60]	13(43.3)	
<b>Marital status</b>			
single	2(6.7)	4(13.3)	0.67
married	28(93.3)	26(86.7)	
<b>Education level</b>			
Illiterate	4(13.3)	1(3.3)	0.50
Elementary	3[10]	7(23.3)	
Middle school	5(16.7)	5(16.7)	
High School	11(36.7)	11(36.7)	
University	7(23.3)	6(20.0)	
<b>Occupation</b>			
Unemployed	2(6.7)	3[10]	0.66
Non-governmental	10(33.3)	12[40]	
Governmental	5(16.7)	7(23.3)	
Housewife	13(43.3)	8(26.7)	
<b>Living setting</b>			
Urban	23(76.7)	25(83.3)	0.74
Rural	7(23.3)	5(16.7)	
<b>Pulmonary Infectious Disease</b>			
yes	14(46.7)	10(33.3)	0.29
no	16(53.3)	20(66.7)	
<b>Treatment History</b>			
yes	13(43.3)	11(36.7)	0.59
no	17(56.7)	19(63.3)	
<b>History of Type of Treatment</b>			
Medical	9[75]	8(27.7)	0.90
Surgical	3[25]	3(27.3)	

Continuous variables reported using mean±SD and categorical variables reported using n(%). P values were calculated based on the t-test and or Chi-squared test.

#### 3.3. Patients' secondary outcomes

##### 3.3.1. Para-clinical results

The baseline and final para-clinical results (laboratory and radiologic findings) are summarized in Table 2. Para-clinical variables refer to laboratory and radiological parameters. The mean SpO2 level had no significant difference between the two arms before the intervention (p = 0.11); but, at the end of the study, the intervention arm showed a significant increase compared to the control arm (P < 0.001). Also, the mean SpO2 level had a significant increase at the end of the study in both arms (p < 0.001) compared with their corresponding baseline values. At the end of the study, both groups showed a significant decrease in the mean percentage of lung involvement on CT scans (p < 0.001), without a significant difference between the groups (p > 0.05). The mean number of lymphocytes was higher in the intervention arm than the control arm at the beginning and end of the study, yet, there was neither a significant difference between the two arms at the beginning (p = 0.15) nor at the end of the study (p = 0.08). However, at the end of the study, a significant decrease in the mean number of lymphocytes was noted in the intervention arm (p = 0.03), and a

**Table 2**  
Comparison of baseline and final Para-clinical results between Intervention and Control arms of the COVID-19 patients.

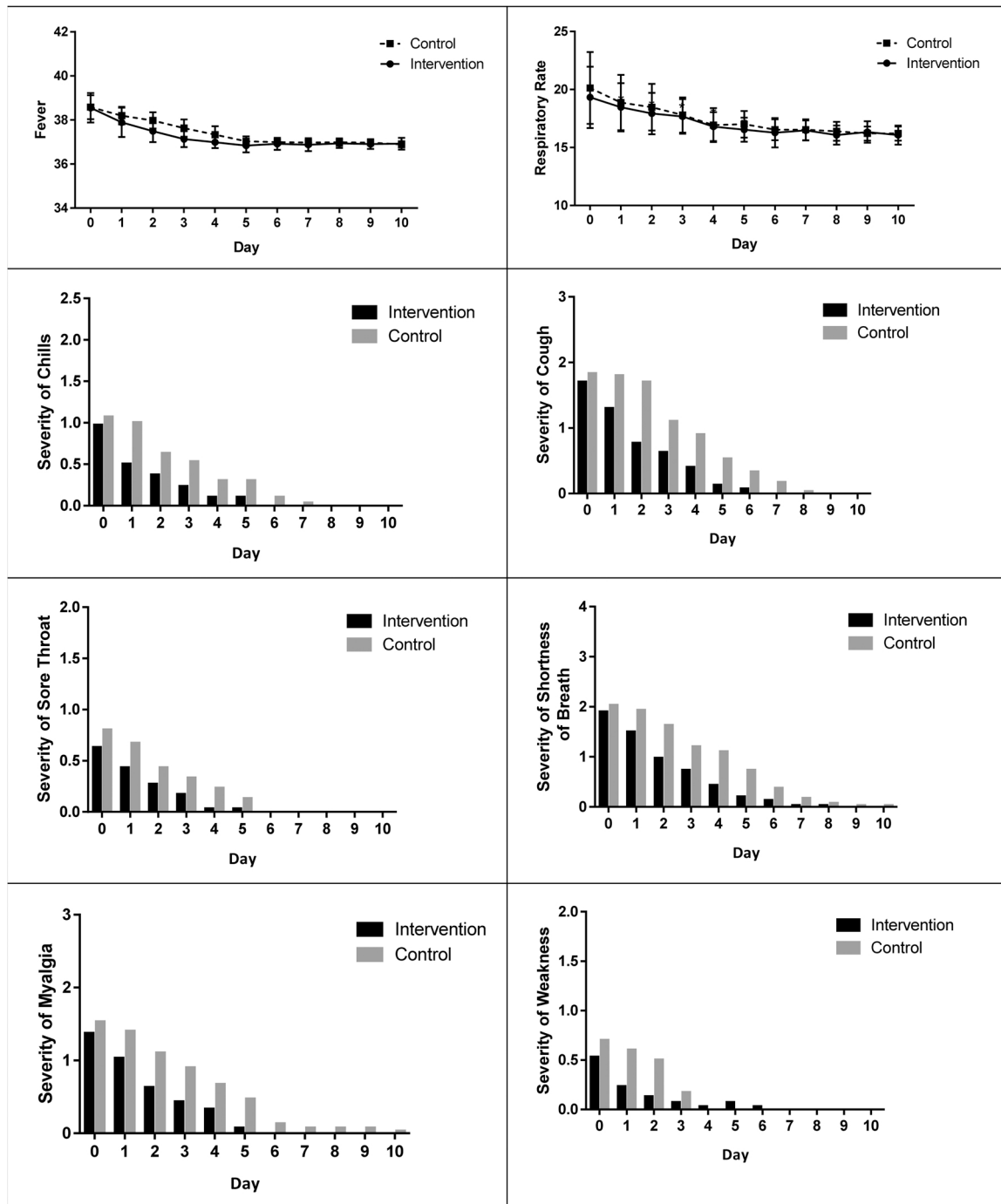
Variable	Trial Arm	Time of Assessment		P-Value
		Baseline	Final	
SpO2	Intervention	92.70±2.67	97.30±1.05	<0.001
	Control	91.57±2.51	95.37±1.40	
	P-Value	0.11	<0.001	
CT findings	Intervention	52±11.86	19.5±9.41	<0.001
	Control	62.33±10.40	40.17±9.24	
	P-Value	0.001	<0.001	
Lymphocyte	Intervention	25.44±7.23	24.50±5.33	0.031
	Control	21.45±3.90	22.36±3.09	
	P-Value	0.15	0.08	
Hb	Intervention	13.56 ±.91	13.65 ±.92	0.004
	Control	13.71 ±.93	13.76 ±.95	
	P-Value	0.52	0.65	
PMN	Intervention	62.87±4.96	60.87±5.06	<0.001
	Control	66.00±3.62	64.23±3.91	
	P-Value	0.01	0.006	
Plt	Intervention	225.10±56.69	226.43±54.55	0.455
	Control	212.83±48.19	209.80±41.95	
	P-Value	0.33	0.18	
ESR	Intervention	25.97±11.44	17.60±7.69	<0.001
	Control	25.53±6.55	19.30±4.67	
	P-Value	0.56	0.21	
CRP	Intervention	Negative 7(23.3) Trace 3[10]1 <sup>+</sup> 12 [40]2 <sup>+</sup> 6[20]3 <sup>+</sup> 2 (6.7)	Negative 23 (76.6)Trace 7 (23.3)	<0.001
	Control	Negative: 3[10] Trace: 1(3.3)1 <sup>+</sup> : 13(43.3)2 <sup>+</sup> : 11 (36.7)3 <sup>+</sup> : 2(6.7)	Negative: 12[40] Trace:14(46.7) 1 <sup>+</sup> : 4(13.3)	
	P-Value	0.42	0.004	
RT-PCR	Intervention	-	Negative RT-PCR 18[60]Positive RT-PCR 12[40]	-
	Control	-	Negative RT-PCR 11(36.7)Positive RT-PCR 19(63.3) 0.07	

Continuous variables reported by mean±SD and categorical variables reported by n(%). P values were calculated based on the independent t-test and or paired t test.

Abbreviations: COVID-19: Coronavirus disease 2019; SpO2: oxygen saturation; SD: standard deviation; CT: computed tomography; Hb: hemoglobin; PMN: polymorphonuclear cells; Plt: platelets; ESR: erythrocyte sedimentation rate; CRP: c reactive protein; RT-PCR: Reverse-transcription Polymerase Chain Reaction. P < 0.05 in bold. Para-clinical results included laboratory and CT-SCAN findings.

significant increase was observed in the control arm ( $p = 0.001$ ). Although the mean Hb level of patients at the beginning and end of the study in the intervention group was lower than in the control group, this difference was not significant ( $p$  values were 0.52 and 0.65, respectively). At the end of the study, a significant decrease in the PMN counts was observed compared with their corresponding baseline values in both arms ( $p < 0.001$ ). However, by adjusting the PMN effect, the mean PMN counts were not significantly different between the two groups

( $p=0.48$ ). The mean number of PLT at the end of the study was not significantly changed in both groups ( $p > 0.05$ ). Although the mean ESR level in the intervention arm was higher at the beginning and less at the end of the study, there was no significant difference between the two arms neither at the beginning ( $p = 0.56$ ) nor at the end of the study ( $p = 0.21$ ). However, at the end of the study, a significant decrease in mean ESR levels was observed in both arms compared to their corresponding baseline values ( $p < 0.001$ ). Furthermore, at the beginning of



**Fig. 2.** Comparison of clinical signs between control and intervention arms of COVID-19 patients, daily Fever and respiratory rate were continuous variables and the rest of variables were ordinal as: no, mild, moderate and severe Based on repeated measure ANOVA, the difference between two groups for fever was significant ( $P = 0.004$ ) but for respiratory rate was not ( $P = 0.297$ ) Based on Generalized Estimating Equations (GEE), the differences between two groups in terms of severity of cough, shortness of breath and myalgia were significant ( $P = 0.001$ ,  $P = 0.004$  and  $0.005$ ) but for severity of chills, sore throat and weakness were not ( $P = 0.059$ ,  $P = 0.220$  and  $P = 0.121$ ) The levels of all variables decreased over time in both groups ( $P < 0.001$ ). Variables into the first and second graphs were continuous while others were ordinal variables. So, the ordinal variables made histogram graphs.

the study, there was no significant difference in the frequency of positive and/or negative CRP results between the two groups ( $p=0.42$ ); but at the end of the study, the frequency of negative CRP results was significantly more evident in the intervention arm ( $P<0.001$ ). In this regard, out of 30 patients belonging to the control arm, 12 patients (40%), 14 patients (46.7%) and 4 (13.3%), had negative, trace, and positive (one plus) CRP at the end of the RCT, respectively. In the intervention group, 23 (76.7%) and 7 (23.3%) patients had negative and trace CRP levels, respectively.

### 3.3.2. Clinical manifestations

Fig. 2 shows a daily comparison of the symptoms of COVID-19 between the control and intervention arms. The mean fever in both groups decreased significantly throughout the time ( $p < 0.001$ ); however, there was a significantly greater reduction in body temperature in the intervention arm compared with the control arm. Based on repeated measure ANOVA [Fig. 2], the difference between the groups regarding fever was significant ( $P = 0.004$ ), but this was not the case regarding the respiratory rate ( $P = 0.29$ ). The severity of chills decreased significantly in both control and intervention arms throughout the time ( $p < 0.001$ ); however, there was no significant difference between the two arms ( $p = 0.06$ ). The severity of cough in both groups had decreased throughout the study ( $p<0.001$ ), and this reduction was significantly less in the intervention arm compared with the controls ( $P=0.001$ ). The severity of sore throat in the control and intervention arms had decreased significantly throughout the investigation ( $p<0.001$ ), without a significant difference between the two arms ( $p=0.22$ ). The severity of shortness of breath in both groups had decreased throughout the trial ( $p<0.001$ ), and this reduction was significantly more in the intervention arm ( $P=0.004$ ). The myalgia intensity had significantly decreased in both groups ( $p<0.001$ ), and this reduction was more significant in the intervention arm ( $P=0.005$ ). The severity of weakness had significantly decreased in both study arms ( $p<0.001$ ), without a significant difference between the two arms ( $p = 0.12$ ).

The mean  $\pm$  SD of LOS in the intervention arm (4.44 days) was significantly shorter than in the control arm (7.18 days;  $P<0.001$ ).

### 3.4. Efficacy and safety

No adverse effects occurred in either the intervention group or the control group.

## 4. Discussion

At the initiation of this RCT, both groups of patients had similar baseline demographics and characteristics regarding medical history. There was no significant difference in RT-PCR results between the groups. All evaluated COVID-19 symptoms decreased significantly in both arms during the study period. However, out of 8 signs, 4 signs had a significant reduction in the intervention arm compared with the control arm, including fever, the severity of cough, shortness of breath and myalgia. Also, at the end of this RCT, out of 8 para-clinical variables, 3 variables had a significant improvement in the intervention arm compared with the control arm, including the mean increase in SpO<sub>2</sub> level, the reduction in the mean percentage of lung involvement on CT scans and the improvement in CRP levels. Also, the LOS in patients who had consumed organic herbal Amla tea was significantly shorter than that of the control group.

In a recent study published by Ul Qamar et al. concerning SARS-CoV-2, out of 32,297 Chinese medicinal compounds, Amla along with eight others have been proposed as novel non-toxic, druggable natural compounds that bind to the enzyme 3-chymotrypsin-like protease (3CLpro) receptor binding site and the catalytic dyad<sup>10</sup>. This enzyme plays a pivotal role in the viral replication process. It breaks down the gene-derived 800 kDa polypeptide of beta-coronaviruses in 11 specific sites and produces a variety of non-structural viral proteins<sup>11,12</sup>. In an

in-vitro study, the antiviral effect of Amla on the herpes simplex virus has been discovered<sup>13</sup>. In another in-vitro study, the antiviral effects of Amla along with six other Thai medical plants have been investigated on the porcine reproductive and respiratory syndrome virus (PRRSV). Amla can inhibit PRRSV infection at a low concentration of 78  $\mu\text{g}/\text{mL}$ . It was also ranked second among plants in terms of antioxidant activity against free radicals<sup>14</sup>. A review study has reported that the therapeutic potential of Amla is due to its spasmolytic, expectorant and antitussive effects<sup>4</sup>. Furthermore, the dose-dependent cough suppressive activity of Amla has been described in an animal study<sup>15</sup>. Although the severity of cough showed a significant decrease compared to corresponding baseline values in both arms at the end of the study, this reduction was significantly more in the intervention arm compared to the control arm. Moreover, other animal studies have reported the antipyretic and analgesic activities of Amla<sup>16,17</sup>. In this regard, although fever and myalgia at the end point of the trial showed a significant decrease compared to their corresponding baseline values in both groups, this reduction was significantly more in the intervention arm compared to the control arm.

### 4.1. Limitations and strengths

The present study has several limitations, including 1) failure to assess adherence and certain clinical findings, e.g., the patients' smoking status and disease complications; 2) prolonged follow-up outcomes after cessation of treatment were not documented; 3) the sample size of this clinical trial was relatively small. This study has the following strengths: firstly, more comprehensive data have been presented in this RCT study compared with other studies. Secondly, this was a double-blind RCT, which is among the most reliable study designs regarding COVID-19. However, outcomes, follow-up findings and laboratory or immunological investigations with repeated chest imaging for all participants, should be evaluated for at least a few months following treatment cessation to give more reliable information about the medicinal effects of this plant on COVID-19. Also, we would suggest the assessment of all these factors in different age subgroups. Finally, although this study was conducted in a single province, other nationwide multicenter studies are recommended to assess additional unknown factors, such as race, geographic location, and climate, which may affect the safety and efficacy of Amla.

## 5. Conclusion

This study revealed no significant difference in final RT-PCR results and or degree of lung involvement on CT scans. But, significant reductions in fever, the severity of cough, shortness of breath, myalgia, LOS, and a significant improvement in SpO<sub>2</sub> and CRP levels were noted in the group treated with Amla. Moreover, no adverse effects were observed. Nevertheless, further studies are needed to examine Amla supplements in light of evolving standards of care as well as its mechanism of action.

### CRediT authorship contribution statement

All authors worked equally and contributed to all parts of the study.

### Declaration of Competing Interest

None.

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