



# Inflawell® improves neutrophil-to-lymphocyte ratio and shortens hospitalization in patients with moderate COVID-19, in a randomized double-blind placebo-controlled clinical trial

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## Abstract

**Aims** COVID-19 is a significant global threat to public health. Despite the availability of vaccines and anti-viral drugs, there is an urgent need for alternative treatments to help prevent and/or manage COVID-19 symptoms and the underlying dysregulated immune response. We hypothesized that administration of Inflawell® syrup, a *Boswellia* extract formulation enriched for boswellic acids (BAs), can reduce the excessive or persistent inflammation and thereby prevent disease progression. BAs are medicinally activated triterpenoids found in the resins of *Boswellia spp.*, and possess an immense therapeutic potential due to their anti-inflammatory and immunoregulatory activities. We investigated the effect of Inflawell® syrup, on moderate COVID-19 patients along with the current standard of care treatment.

**Methods** A randomized placebo-controlled double-blind clinical trial was conducted, following definitive confirmation of COVID-19. Forty-seven hospitalized patients with moderate COVID-19 were enrolled and received either the Inflawell® syrup or placebo. Clinical symptoms and markers of inflammation were evaluated at baseline and completion of the trial.

**Results** Our clinical trial revealed an increase in the percentage of oxygen saturation level in patients that received the BAs compared to placebo ( $P < 0.0001$ ). In addition, the average duration of hospitalization was significantly shorter in the BAs group compared with the placebo group ( $P < 0.04$ ). Concomitantly, some improvement in the clinical symptoms including cough, dyspnea, myalgia, headache, and olfactory and gustatory dysfunction were detected in the BAs group. Hematologic findings showed a significant decrease in the percentage of neutrophils ( $P < 0.006$ ) and neutrophil-to-lymphocyte ratio (NLR) levels ( $P < 0.003$ ), associated with a significant increase in the percentage of lymphocytes in the BAs group compared with the placebo ( $P < 0.002$ ). Additionally, a significant decrease in CRP, LDH, IL-6 and TNF- $\alpha$  levels was detected in the BAs group. Following the intervention, fewer patients in the BAs group were PCR-positive for COVID-19 compared to placebo, though not statistically significant.

**Conclusion** Overall, the treatment with Inflawell® resulted in shorter hospital stay, alleviation of COVID-19 clinical symptoms and decline in the level of pro-inflammatory cytokines.

**Trial registration** The trial has been registered in <https://www.irct.ir> with unique identifier: IRCT20170315033086N10 (<https://en.irct.ir/trial/51631>). IRCT is a primary registry in the WHO registry network (<https://www.who.int/clinical-trials-registry-platform/network/primary-registries>).

**Keywords** COVID-19 · Clinical trial · Boswellic acids · Inflammation · Inflawell® syrup · NLR

## Introduction

The global COVID-19 pandemic has resulted in a large number of hospitalization and death due to a lack of effective treatments to manage COVID-19 symptoms. SARS-CoV2 infection, triggers a variable immune response and clinical

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symptoms ranging from benign and asymptomatic to rapidly progressing symptoms leading to acute respiratory distress syndrome (ARDS) (Hoehl et al. 2020; Grasselli et al. 2020). The primary immune response against SARS-CoV2 involves activation of the innate immune system including recruitment of monocytes-macrophages, neutrophils, natural killer cells and the release of interferons (IFNs), pro-inflammatory cytokines, and chemokines to coordinate an antiviral and cytotoxic response against the viral invasion (Boechat et al. 2021). Hyper-induction of inflammatory cytokines mainly IL-1 $\beta$ , IL-6 and TNF- $\alpha$  produced by innate and adaptive immune cells is one key aspect of COVID-19 that can lead to cytokine release syndrome (Olbei et al. 2021; Costela-Ruiz et al. 2020). Concomitantly, SARS-CoV2 induces the release of chemokines that recruit neutrophils to the affected organs. An aberrant neutrophil activation in severe COVID-19 patients results in excessive neutrophil tissue infiltration and formation of neutrophil extracellular traps (NETs) in a process called NETosis that may lead to lung injury in these patients (Zuo et al. 2020; Wang et al. 2020). A high neutrophil-to-lymphocyte ratio (NLR) as well as T cell lymphopenia, especially decreased CD4+ T cells have been reported in the majority of COVID-19 patients and particularly among the severe cases (Peng et al. 2020). In concert with these findings, NLR has been indicated as an independent risk factor for severe COVID-19 (Alkhatip et al. 2021; Cai et al. 2021; Zeng et al. 2021; Liu et al. 2020). Considering the important role of pro-inflammatory pathways in COVID-19 pathology, several natural compounds with anti-inflammatory and immunomodulatory effects have been proposed as potential adjunctive therapy in conjunction with anti-viral drugs used in the current standard of care treatment (Ho et al. 2021). There is a large body of evidence suggesting that Boswellic acids (BAs), the main pharmacologically active triterpenoids derived from the resin of *Boswellia spp.*, confer medicinal effect(s) due to their anti-inflammatory, immunomodulatory and antioxidant properties (Du et al. 2015; Gomaa et al. 2021). The anti-inflammatory properties of BAs are exerted through inhibition of cyclooxygenase-2, 5-lipoxygenase, inducible NO synthase and modulation of nuclear factor kappa B family of transcription factors (Baram 2019; Roy et al. 2019). In-silico studies have demonstrated binding of BAs to the spike protein and RNA polymerase of SARS-CoV2 suggesting that BAs may inhibit the viral cell entry and replication (Caliebe et al. 2021; Kadhim et al. 2021). Therefore, BAs not only provide anti-inflammatory benefits but may also render antiviral activity, further supporting their use for the prevention or treatment of COVID-19.

Here we studied the effect of BAs, formulated as Inflawell<sup>®</sup> syrup, for adjunctive therapy to support body's immune response against SARS-CoV2 infection. We conducted a phase II randomized, double-blind,

placebo-controlled trial to study the beneficial effect of BAs on the immune system of patients with moderate COVID-19.

## Methods

### Study design and randomization

A phase II randomized, double-blind, placebo-controlled parallel trial was conducted at a single site from January 25 to March 5, 2021. Hospitalized COVID-19 patients ageing  $\geq 18$  years and determined to be PCR positive were enrolled in this study. They showed at least one of these clinical manifestations: (1) respiratory distress (breathing at  $\geq 25$  times per minute), (2) percentage of oxygen saturation level at rest being  $\leq 92\%$ , and (3) having fever. Subsequent to the initial screening, patients were evaluated for the following exclusion criteria: (1) having a history of liver, kidney, and/or heart failure, (2) inability to take the oral medication, (3) pregnancy and lactation or having a positive pregnancy test, (4) participation in two or more clinical studies simultaneously, (5) admission to intensive care unit (ICU), and (6) cancer diagnosis at the time of COVID-19 infection. Randomization was performed based on the four-sized block approach (Suresh 2011). To allocate patients into the two intervention groups, a non-ordering computer sequence code list was generated. Random allocation codes were concealed in envelopes with medication jars and referral sequences. Patients received allocation codes according to the patient referral sequences, and entered into the study. All study participants and researchers were blinded from treatment assignments until the end of the study and all processes were monitored by the study coordinator to ensure the integrity of the process.

### Test material

A *Boswellia* extract formulation, Inflawell<sup>®</sup> syrup developed at Kondor Pharma Inc. (Canada) was used in this study. Each serving (10 ml) of Inflawell<sup>®</sup> syrup consists of 333 mg of *Boswellia serrata* resin extract standardized to contain 40% boswellic acids (K-Vie<sup>™</sup> formulation) dissolved in coconut oil and water. The placebo was prepared by dissolving fructose in coconut oil and water and color was matched by the addition of food coloring.

### Intervention

Following patient recruitment, eligible subjects were randomly allocated to two groups: Inflawell<sup>®</sup> intervention group (BAs group) that received 10 ml of Inflawell<sup>®</sup> syrup thrice daily (30 ml/day), and the control group (placebo group) that received the placebo syrup. Bottles were the

same in shape and size. Inflawell® and placebo syrups were administered along with the standard COVID-19 medications in both groups and patients' symptoms were followed for 14 days. The volume of remaining syrup in the bottles was recorded weekly to confirm the patient's compliance.

### Clinical data, specimen collection, and evaluation of outcome

Patients were examined at the onset of the study and on day 14. Demographic data, physical status including height and body weight, body mass index (BMI), body temperature, were recorder. In addition, the heart and respiratory rates and peripheral venous blood oxygen saturation value, SpO<sub>2</sub>, as well as the medical history and medications were recorded. Blood samples were obtained at day 0 and 14 and serum was immediately collected by centrifugation at 3000 rpm, at 4 °C for 10 min and stored at – 80 °C for further evaluation of the secondary outcomes. The following blood markers were measured: complete blood count (CBC), C-reactive protein (CRP), creatinine, lactate dehydrogenase (LDH), alanine amino transferase (ALT), creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR) (mm/h), prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR). Serum levels of IL-1 $\beta$ , IL-6, TNF- $\alpha$  and IL-10 were also measured twice at each time point using sandwich-type enzyme-linked immunosorbent assay (ELISA). Human assay kits were purchased from Abcam (Cambridge, UK) and International GmbH, IBL (Hamburg, Germany). SARS-CoV-2 RT-PCR test was performed on days 0 and 14 on the nasopharyngeal samples. In this study, the primary endpoint was the duration of hospitalization and the secondary endpoints were levels of CRP, LDH, IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IL-10 and SARS-CoV-2 PCR result at day 14 post treatment.

### Statistical analysis

Data were analyzed using IBM SPSS and GraphPad Prism software. Normal distribution was assessed using Kolmogorov–Smirnov test. Quantitative variables were shown as mean  $\pm$  standard error of mean (SEM). Unpaired *t* test or Mann–Whitney *U* test was used for baseline quantitative variables according to parametric or nonparametric analysis, respectively. Comparative variation of dependent variables was measured by analysis of covariance (ANCOVA). For imbalance adjustment of pre-test data, the baseline of each parameter was used as a covariate and *P* value  $\leq 0.05$  was considered to be statistically significant. Qualitative variables were analyzed using the Chi-Square test.

### Ethics statement

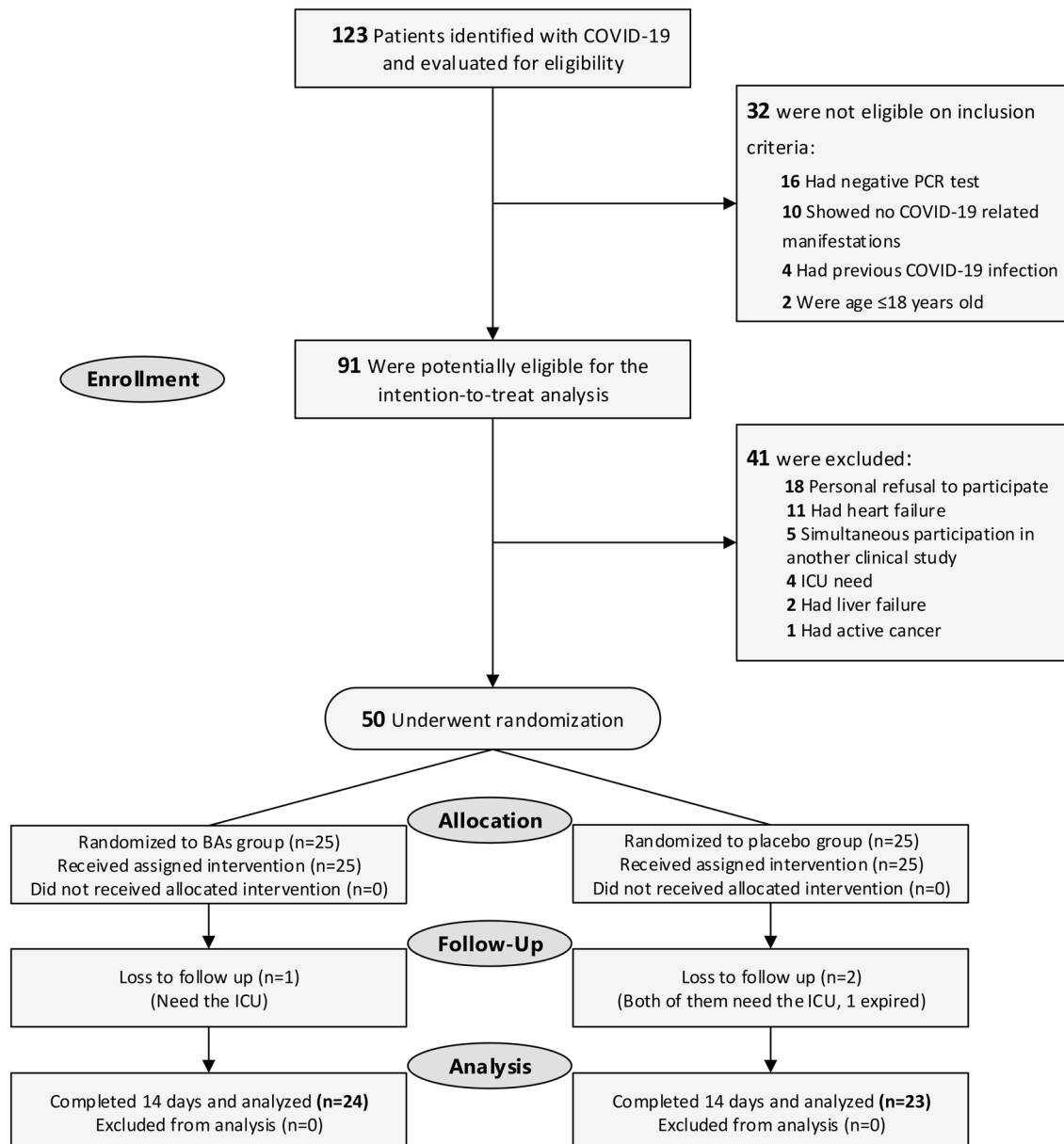
The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (SBMU), Reference number: IR.SBMU.MSP.REC.1399.311, dated 2020-10-13. The trial has been registered in <https://www.irct.ir> with unique identifier: IRCT20170315033086N10 (<https://en.irct.ir/trial/51631>). IRCT is a primary registry in the WHO registry network (<https://www.who.int/clinical-trials-registry-platform/network/primary-registries>). Written and signed informed consent was obtained from all patients.

### Results

Out of 123 patients initially screened for the study at the Tehran University of Medical Sciences Hospital, 32 patients (26%) did not meet the eligibility criteria due to having negative RT-PCR test (16 patients), showing no typical COVID-19 symptoms (10 patients), previous COVID-19 infection (4 patients), and not fitting the age demographic range (2 patients). The rest (74%) were potentially eligible for enrollment. Among eligible subjects, 41 patients were excluded due to: refusing to participate in the study (18 patients), active cancer (1 patient), and simultaneous participation in another clinical study (5 patients), being transferred to ICU (4 patients), suffering from liver and heart failures (2 and 11 patients, respectively). The remaining 50 patients met all enrollment criteria and were assigned to Inflawell® syrup/BAs (*n* = 25) and placebo (*n* = 25) groups. During the trial, 3 additional patients were removed from the study due to aggravation of symptoms and needing to be moved to ICU. Hence, the final number of patients in each group was 24 patients in the BAs group, and 23 patients in the placebo group. All patients continued receiving the standard treatments during the 14-day period (Fig. 1).

### Demographical characteristics and comorbidities

The mean age of participants in BAs and placebo groups was 51.92 yrs (31–76 yrs) and 55.84 yrs (35–78 yrs), respectively (Table 1). The mean BMI was  $27.58 \pm 0.71$  for the BAs group and  $28.05 \pm 0.57$  for the placebo group. While 22 patients (44%) had no clinical history, 28 patients (56%) had at least one comorbidity. The most common comorbidities were diabetes mellitus (28%) and hypertension (22%). In addition, 6% had hypothyroidism, 2% had the chronic obstructive pulmonary disease (COPD), 2% had asthma and 2% had ischemic heart disease (Table 1). Among enrolled patients, one patient treated with BAs and



**Fig. 1** Flow diagram of participants in a Randomized Clinical Trial of BAs group vs placebo group

two placebo-administrated subjects were removed from the study due to admittance to ICU (Fig. 2).

### Clinical outcomes

The most common symptoms reported at the onset of the study were body pain (43 patients, 91.5%) and headache (34 patients, 72.3%), followed by shortness of breath (47 patients, 100%), cough (46 patients, 97.9%), and olfactory/gustatory sense dysfunction (8 patients, 17.02% and 5 patients, 10.63%, respectively). After intervention, the clinical manifestations were improved in both groups but

as shown in Tables 2 and 3, improvement in patients in the BAs group was markedly greater than placebo. Furthermore, the increase in oxygen saturation was significantly greater in the BAs group compared with the placebo group on day 14 (96 vs 93%, with a  $P < 0.0001$ , Table 2). As shown in Table 3, post intervention, the olfactory and gustatory disorders improved in both BAs group and placebo group. While three patients in the placebo group reported to have a loss of olfactory sense with two having gustatory problems that did not improve at day 14, all patients in the BAs group expressed improvement in both senses at the completion of the study. The average days of hospitalization for BAs group

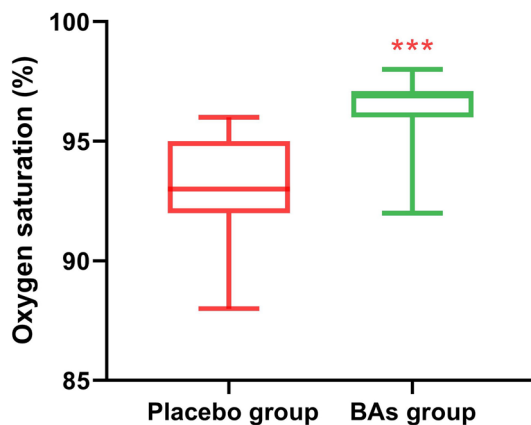
**Table 1** Demographical characteristics, and comorbidities of the patients at baseline

	BAs group (n=25)	Placebo group (n=25)
<i>A. Demographic variables</i>		
Age <sup>a</sup>	51.92 ± 2.66, (31–76)	55.84 ± 2.48, (35–78)
Male—no. (%) <sup>b</sup>	10 (40)	16 (64)
Female—no. (%) <sup>b</sup>	15 (60)	9 (36)
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	27.58 ± 0.71	28.05 ± 0.57
BMI ≥ 30—no. (%) <sup>b</sup>	5 (20)	7 (28)
<i>B. Comorbidities</i>		
Hypertension—no. (%) <sup>b</sup>	6 (24)	5 (20)
DM—no. (%) <sup>b</sup>	5 (20)	9 (36)
Ischemic heart disease—no. (%) <sup>b</sup>	0	1 (4)
Asthma—no. (%) <sup>b</sup>	0	1 (4)
COPD—no. (%) <sup>b</sup>	1 (4)	0
Hypothyroidism—no. (%) <sup>b</sup>	2 (8)	1 (4)
<i>C. Intensive care need</i>		
ICU admission (%) <sup>b</sup>	1 (4)	2 (8)

BMI Body Mass Index, DM Diabetes Mellitus, COPD Chronic Obstructive Pulmonary Disease, ICU Intensive care unit

<sup>a</sup>Values are given as the mean ± SEM

<sup>b</sup>Values are given as the number of patients (%)



**Fig. 2** Change of oxygen saturation in BAs group and placebo group after the intervention (day 14). Data is presented as mean ± SEM and was analyzed using ANCOVA test.  $P < 0.05$  was considered significant

were shorter compared to the placebo group ( $4.20 \pm 0.68$  vs.  $5.15 \pm 0.45$  days,  $P < 0.04$ ) (Table 4, Fig. 3).

### Laboratory findings

All COVID-19 patients in the study showed an elevated level of neutrophils, NLR, CRP, LDH, and ESR and a decrease in lymphocytes at baseline. Following the 14 days of treatment, hematological results showed that NLR was significantly reduced in the BAs group ( $2.74 \pm 0.37$ )

compared to the placebo group ( $4.61 \pm 0.60$ ) ( $P < 0.003$ ). Conversely, the lymphocyte count in the BAs group was significantly increased in comparison with the placebo group ( $P < 0.002$ ) (Table 5 and Fig. 4). The levels of CRP and LDH significantly declined at day 14 in the BAs group compared to the placebo received patients ( $P < 0.03$  and  $P < 0.04$ , respectively). Despite a decreasing trend in ESR and ALT in the BAs group, the difference was not statistically significant in comparison to the placebo group ( $P = 0.164$  and  $P = 128$ , respectively). No significant changes were seen in other parameters.

### Effect of BAs treatment on pro/anti-inflammatory mediators

The serum concentrations of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were measured at days 0 and 14. The mean level of IL-6 in the BAs group ( $3.26 \pm 0.41$ ) was significantly lower than the placebo group ( $5.63 \pm 0.51$ ) ( $P < 0.001$ ). A significant difference was also detected in the serum concentration of TNF- $\alpha$  in the BAs group ( $69.9 \pm 3.51$ ) compared to the placebo group ( $93.05 \pm 6.05$ ) ( $P < 0.0001$ ). No significant intergroup change was observed in IL-1 $\beta$  levels ( $P = 0.124$ ). IL-10 level showed an increase in the BAs group over the course of the treatment ( $14.48 \pm 5.221$ ) while it did not change significantly in the placebo group ( $7.605 \pm 1.957$ ) after 14 days ( $P = 0.18$ ) (Table 6).

**Table 2** Symptoms of COVID-19 patients in BAs group and placebo group at the baseline and day 14

Physical examinations	BAs group (n=24)		Placebo group (n=23)		P value*
	Baseline	Day 14	Baseline	Day 14	
Body temperature (°C) <sup>a</sup>	37.31 ± 0.16	36.40 ± 0.04	37.33 ± 0.19	36.50 ± 0.05	0.201
Heart rate (n) <sup>a</sup>	85.33 ± 2.18	78.58 ± 0.92	81.09 ± 1.85	80.57 ± 1.11	0.19
Oxygen saturation (%) <sup>a</sup>	91.50 ± 0.63	96.00 ± 0.38	90.83 ± 0.35	93.35 ± 0.39	0.0001
Cough (%) <sup>b</sup>	24 (100)	2 (8.3)	22 (95.6)	4 (17.4)	–
Shortness of breath (%) <sup>b</sup>	24 (100)	4 (16.6)	23 (100)	8 (30.4)	–
Body pain (%) <sup>b</sup>	23 (95.8)	0 (0)	20 (86.9)	3 (17.39)	–
Headache (%) <sup>b</sup>	18 (75)	1 (4.2)	16 (69.5)	1 (4.3)	–

Data were analyzed using ANCOVA test and  $P < 0.05$  was considered significant

<sup>a</sup>Values are given as the mean ± SEM<sup>w</sup>

<sup>b</sup>Values are given as the number of patients (%)

**Table 3** Recovery of olfactory and gustatory sense in COVID-19 patients in BAs group and placebo group at the baseline and day 14

Outcome	BAs group (n=24)		Placebo group (n=23)	
	Baseline	Day 14	Baseline	Day 14
<b>Olfactory sense</b>				
Normal	19 (79.1%)	24 (100%)	20 (86.9%)	20 (86.9%)
Moderate	0 (0%)	0 (0%)	0 (0%)	3 (13.0%)
Weak	5 (20.8%)	0 (0%)	3 (%)	0 (0%)
<b>Gustatory sense</b>				
Normal	21 (87.5%)	24 (100%)	21 (91.3%)	21 (91.3%)
Moderate	0 (0%)	0 (0%)	0 (0%)	2 (8.7%)
Weak	3 (12.5%)	0 (0%)	2 (8.7%)	0 (0%)

Values are given as the number of patients (%)

**Table 4** Length of hospitalization, as the main primary outcome

	BAs group (n=24)	Placebo group (n=23)	P value*
Hospital stay	4.20 ± 0.68	5.15 ± 0.45	0.04

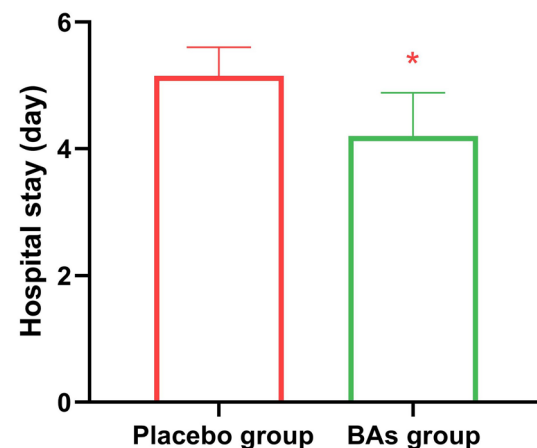
Values are given as the mean ± SEM. Data were analyzed using *t* test and  $P < 0.05$  was considered significant

### Effect of BAs treatment on SARS-CoV-2 RT-PCR test

All enrolled individuals had positive RT-PCR test for SARS-CoV-2 at day 0. After the intervention (day 14), 70.83% of the patients in the BAs group had a negative test result whereas in the placebo group only 47.8% were tested negative, however, the difference between the two groups was not statistically significant ( $P = 0.108$ ) (Fig. 5; Table 7).

## Discussion

Despite the current widespread vaccination and use of anti-viral drugs, the management of COVID-19 symptoms remains challenging. Using herbal medicines to improve

**Fig. 3** Comparison of the length of hospital stay in BAs and placebo groups. Data are presented as mean ± SEM and was analyzed using *t* test.  $P < 0.05$  was considered significant

immune response to SARS-CoV2 infection alongside the current standard of care might provide a viable approach for adjunctive therapy. In addition, the application of safe and effective herbal medicines standardized for active compounds could hinder the spread of SARS-CoV2 among a percentage of the population that oppose vaccination. Several natural and herbal compounds with anti-inflammatory and anti-viral activities have been suggested for COVID-19 treatment (Singh et al. 2021; Li et al. 2021), but limited clinical trial data exists to support their broad applications. In the present study, we used Inflawell<sup>®</sup> syrup, a formulation comprising Boswellia extract enriched for Boswellic acids (BAs), on moderate COVID-19 patients. The average length of hospitalization was measured as the primary endpoint while viral count (PCR positivity at day 14), NLR, as well as several infections and inflammation markers were evaluated as secondary outcomes. Our study revealed a significantly shorter length of hospital stay in patients treated with BAs compared with placebo. This is a significant finding as such

**Table 5** Level of blood biomarkers of patients in BAs and placebo groups at baseline and day 14th

Laboratory tests results	BAs group (n=24)		Placebo group (n=23)		P value*
	Baseline	Day 14	Baseline	Day 14	
WBC count (× 1000/uL)	7.62 ± 0.56	7.81 ± 0.62	7.31 ± 0.56	8.90 ± 0.47	0.056
Neutrophil (%)	78.37 ± 2.29	62.80 ± 2.17	75.86 ± 2.12	70.27 ± 2.40	0.006
Lymphocyte (%)	17.09 ± 2.01	28.41 ± 2.01	19.02 ± 1.73	20.74 ± 2.10	0.002
NLR	6.45 ± 0.77	2.74 ± 0.37	5.43 ± 0.90	4.61 ± 0.60	0.003
ESR (mm/H)	61.79 ± 4.88	26.75 ± 3.85	51.30 ± 4.76	30.83 ± 4.18	0.164
CRP (mg/L)	94.89 ± 10.25	9.83 ± 3.01	75.17 ± 10.30	23.67 ± 8.28	0.034
LDH (U/L)	550.5 ± 54.41	207.5 ± 10.92	595.1 ± 50.89	251.5 ± 16.79	0.04
ALT (U/L)	42.17 ± 6.10	32.21 ± 4.05	35.13 ± 3.84	39.35 ± 6.19	0.128
PT (s)	12.63 ± 0.10	13.10 ± 0.17	13.54 ± 0.51	14.51 ± 1.17	0.653
PTT (s)	30.33 ± 0.68	33.46 ± 1.01	30.00 ± 0.65	32.91 ± 1.33	0.717
INR	1.04 ± 0.01	1.03 ± 0.01	1.12 ± 0.04	1.17 ± 0.09	0.89
Creatinine (mg/dL)	1.13 ± 0.25	0.90 ± 0.02	0.96 ± 0.05	0.89 ± 0.02	0.86
CPK(U/L)	94.83 ± 10.33	69.00 ± 12.57	99.87 ± 11.63	49.26 ± 4.75	0.15

WBC white blood cell, NLR neutrophil/lymphocyte ratio, ESR Erythrocyte sedimentation rate, CRP C-reactive protein, LDH lactate dehydrogenase, ALT alanine aminotransferase, PT prothrombin time, PTT partial thromboplastin time, INR international normalized ratio, CPK creatine phosphokinase

Data are presented as mean ± SEM and were analyzed using ANCOVA test and  $P < 0.05$  was considered significant

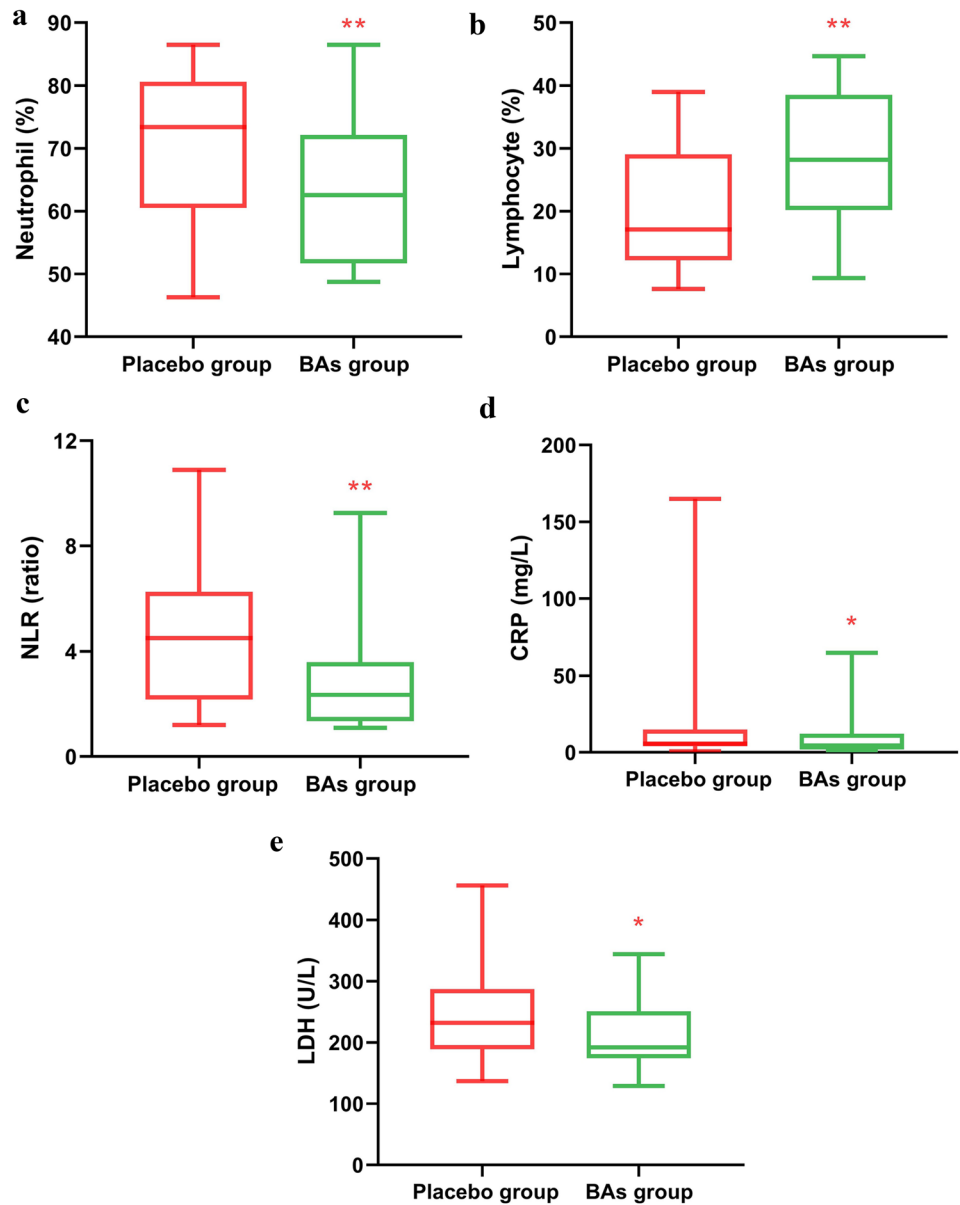
intervention could reduce the current burden on hospitals and the cluttering of the health care system due to the high volume of COVID-19 hospitalizations. In agreement with a shorter length of hospitalization, the patients receiving Inflawell® demonstrated a slightly larger drop in the number of PCR positive cases after 14 days of treatment. The difference, however, was not statistically significant when compared to the placebo group. Due to the rather small sample size in our study, the observed results cannot be accurately attributed to reported antiviral properties of BAs. Nevertheless, negative PCR results compared with the control, could be correlated to immunoregulatory properties.

Moreover, the patients receiving the BAs (Inflawell® group) showed improvement in the clinical symptoms including olfactory and gustatory dysfunction, shortness of breath, cough, body pain and headache. Recent studies have indicated a correlation between the loss of olfactory and gustatory senses with an increase in the feeling of loneliness, depression and anxiety in COVID-19 patients (Kooper 2021; Dudine et al. 2021). Therefore, a faster relief from these symptoms could positively impact patients' quality of life. Studies have shown that neuroinflammation and the subsequent microglial activation in olfactory pathways along with necrosis in the olfactory bulb is a key player in COVID-19 anosmia (Laurendon et al. 2020; D'Ascanio et al. 2021). In addition, gustatory dysfunction has been shown to be associated with the secretion of inflammatory cytokines from the taste bud cells leading to impairment in the gustatory sense (Cazzolla et al. 2020). The anti-inflammatory activity of the Inflawell® syrup containing BAs might explain

the alleviation of the olfactory and gustatory symptoms in our study. A recent clinical trial on the effect of two other anti-inflammatory compounds, palmitoylethanolamide (PEA) and luteolin in COVID-19 patients has demonstrated a similar improvement in the olfactory and gustatory senses of these patients further confirming the benefits of anti-inflammatory compounds for managing these symptoms (D'Ascanio et al. 2021).

The immune response to SARS-CoV2 infection is rather complex and not completely elucidated. In this study, we measured the level of several markers of immune response and inflammation. Assessment of the percentages of neutrophil, lymphocyte and NLR in the BAs group receiving Inflawell® syrup showed an increase in the number of lymphocytes while neutrophil counts and NLR values were reduced compared with placebo. NLR is an independent risk factor of disease severity in COVID-19 patients (Reusch et al. 2021; Hazeldine and Lord 2021). Over-activation of neutrophils and their infiltration into the lung can be detrimental for COVID-19 patients and further result in lung injury and ARDS (Yang et al. 2021; Hazeldine and Lord 2021). In addition, a low lymphocyte count (lymphopenia) has been associated with COVID-19 symptoms (Kong et al. 2020; Ghizlane et al. 2021). The improvement of NLR in patients that were treated with BAs suggests the immunomodulatory effect of these compounds. Variation in NLR can be monitored to effectively assess the efficacy of treatment. A recent study using Shenhuang Granule (SHG), on COVID-19 patients reported similar improvements in NLR and reduction in the clinical symptoms (Zhou et al. 2021).

**Fig. 4** **A** Neutrophil percent, **B** Lymphocyte percent, **C** NLR, **D** the levels of CRP, and **E** LDH, day 14 post-intervention in both BAs group and placebo group. Data are presented as mean  $\pm$  SEM and were analyzed using ANCOVA test.  $P < 0.05$  was considered significant



**Table 6** Levels of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and IL-10 (pg/mL) in BAs group and placebo group at the baseline and day 14

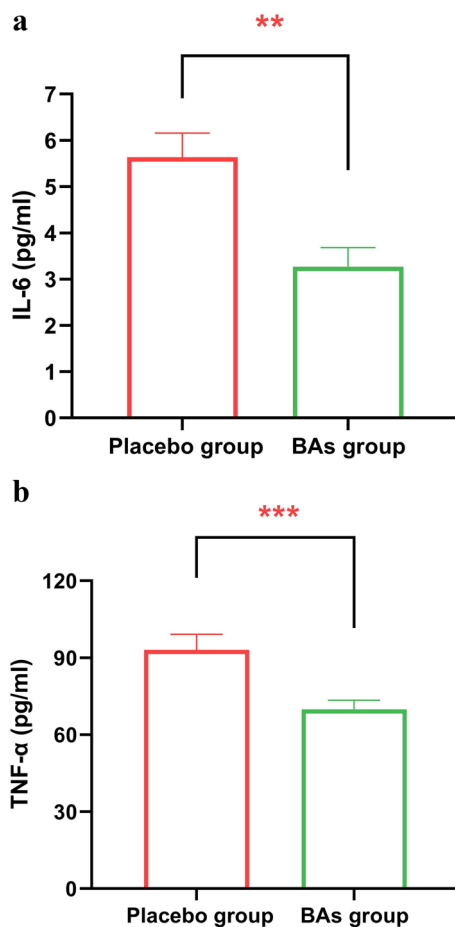
Factors (pg/mL)	BAs group (n=24)		Placebo group (n=23)		P value*
	Baseline	Day 14	Baseline	Day 14	
IL-1 $\beta$	4.081 $\pm$ 0.655	2.020 $\pm$ 0.359	0.413 $\pm$ 0.334	3.809 $\pm$ 0.825	0.124
IL-6	11.21 $\pm$ 1.379	3.268 $\pm$ 0.415	4.880 $\pm$ 0.683	5.638 $\pm$ 0.518	0.001
TNF- $\alpha$	79.79 $\pm$ 4.509	69.90 $\pm$ 3.513	79.78 $\pm$ 3.996	93.05 $\pm$ 6.051	0.0001
IL-10	4.346 $\pm$ 1.412	14.48 $\pm$ 5.221	12.61 $\pm$ 3.038	7.605 $\pm$ 1.957	0.18

Data are presented as mean  $\pm$  SEM and were analyzed using ANCOVA test and  $P < 0.05$  was considered significant

In another clinical trial, Viranorm, a formulation composed of six herbal ingredients, was used every six hours as an add-on treatment on asymptomatic mild COVID-19 patients. Their results also demonstrated a decrease of NLR following

administration for 14 days concomitant with improvement in clinical symptoms (Padmanaban 2021). Altogether, these findings support the use of Inflawell<sup>®</sup> to improve NLR and manage symptoms of COVID-19.





**Fig. 5** Levels of inflammatory cytokines at day 14 post-intervention in both BAs and placebo groups. Data are presented as mean  $\pm$  SEM and were analyzed using ANCOVA test.  $P < 0.05$  was considered significant

**Table 7** Comparing outcomes of RT-PCR test in BAs and placebo groups at the baseline and 14th day

RT-PCR	BAs group (n = 24)		Placebo group (n = 23)		P value*
	Baseline	Day 14	Baseline	Day 14	
Positive	24 (100%)	7 (29.2%)	23 (100%)	12 (52.2%)	0.108
Negative	0 (0%)	17 (70.83%)	0 (0%)	11 (47.8%)	

Values are given as the number of patients (%)

P value were calculated using chi-square and  $P < 0.05$  was considered as significant

In our study, the levels of CRP and LDH drastically reduced after administration of Inflawell® syrup for 14 days. The serum levels of CRP and LDH have been reported to increase in COVID-19 (Dogan et al. 2021;

Poggiali et al. 2020; Wang et al. 2004). CRP is a commonly used marker for infection and inflammation (Sproston and Ashworth 2018) and an elevated LDH has been associated with increased odds of severe COVID-19 disease (Henry et al. 2020). The observed decline in CRP and LDH levels in our study could be attributed to anti-inflammatory effects of BAs in Inflawell® syrup that regulate and balance the inflammatory processes.

Uncontrolled overproduction of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$  in COVID-19 could lead to cytokine release syndrome and subsequently to acute pulmonary damage, multiple organ failure, and ultimately death (Pum et al. 2021; Catanzaro et al. 2020; Mahat et al. 2021). In our study, the levels of IL-6 and TNF- $\alpha$  showed a statistically significant decline following the two-week treatment with Inflawell® syrup that may explain the faster patient recovery in the treatment group. IL-6 is one of the key pro-inflammatory cytokines associated with the exacerbation of COVID-19 symptoms and has been a target for anti-IL-6 antibody therapy (Matthay and Luetkemeyer 2021). Our study suggests that Inflawell® can effectively lower the level of IL-6 thereby providing a supplement or alternative to antibody therapy for the management of COVID-19 symptoms.

## Conclusion

In summary, our study supports the benefit of BAs formulated as Inflawell® syrup, as a supportive treatment leading to shorter hospitalization and alleviation of some of the clinical symptoms and inflammatory biomarkers associated with COVID-19. A larger multi-center clinical trial, however, would be needed to confirm and expand on the findings.

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**Data availability** The enquiries about data availability should be directed to the corresponding author.

## Declarations

**Conflict of interest** The authors declare that there is no conflict of interest.


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