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The Effect of Bromelain Combined With Montelukast in Hospitalized COVID-19 Patients

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Abstract

Introduction: The activation of bradykinin B1 receptors on endothelial cells in the lung following inflammation is a major cause of the severity and mortality of COVID-19. It has already been shown that bromelain and montelukast as two anti-inflammatory agents can be effective in controlling this condition.

Methods: Patients with the novel coronavirus (COVID-19) referred to Masih Daneshvari hospital in Tehran were included in the study after providing full explanations and obtaining written consent. All 40 patients with moderate symptoms were randomly divided into the placebo (n=20) and intervention (n=20) groups. In the sample group, a dose of 200 mg oral bromelain was given to patients every 8 hours and one tablet of montelukast 10 mg 1 hour before or after dinner for 5 days. In the control group, placebo capsules were administered exactly at the above intervals. The results were evaluated using a *t* test and SPSS21 software.

Results: After treatment, the sample (bromelain and montelukast) group represented significant improvements in *C-reactive protein* (CRP), lactate dehydrogenase (LDH), and lymphocyte count ($P<0.05$), while the other factors did not have significant differences with the control group.

Conclusion: Bromelain and montelukast can improve the condition of hospitalized COVID-19 patients by the positive effect on oxygen saturation, lymphocytes, serum levels of CRP, and LDH.

Keywords: Bromelain, Montelukast, COVID-19, Inflammatory response, Clinical symptoms, Respiratory parameters, Immunological factors

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Introduction

With the prevalence of SARS-CoV 2 infection, known as COVID-19, the challenge of treating and providing treatment options for patients has always been a priority for treatment teams.[1-3]

This infection causes localized pulmonary angioedema, which in turn increases the influx of local immune cells and proinflammatory cytokines into the edematous area.[4,5] This type of bradykinin-dependent angioedema via B1 and B2 receptors is an important feature of SARS-CoV-2.[6,7]

The expression of bradykinin B1 and B2 receptors can be induced by inflammatory mediators (e.g., *interleukin* [IL-4], IL-13, *tumor necrosis factor*-α, IL-6, and IL-8) via intracellular mitogen-activated protein kinase and nuclear factor kappa B (NF-κB) signaling.[8-10] BK expresses its therapeutic effects, mainly vasodilation, by activating B2 receptors.[11]

The excessive activity of coagulation factors can have devastating effects through thrombotic disorders.[12] COVID-19-associated coagulation is characterized by increased D-dimer, fibrinogen, systemic thrombotic complications in venous and arterial vessels, and decreased prothrombin time.[13] Thus, anticoagulants or thrombotic therapies provide an opportunity to prevent or reduce the "excessive" production of thrombin while maintaining homeostasis.

Bromelain obtained from raw pineapple extract is an anti-inflammatory that is involved in reducing the serum and tissue levels of quinogen and bradykinin.[14,15] Due to its anti-edematous, anti-inflammatory, and inhibitory properties, bromelain has been useful for the treatment of many diseases such as bronchitis, sinusitis, arthritis, and inflammation reduction.[16] More precisely, these effects are due to increased serum fibrinolytic activity and inhibition of fibrinogen synthesis, as well as direct degradation of

fibrin and fibrinogen.[13] On the other hand, this drug potentially activates the immune system in connection with a rapid response to cellular stress.[17] Conversely, bromelain reduces the secretion of cytokines when immune cells are already stimulated by inflammatory conditions caused by cytokine production.

Montelukast is a selective cysteinyl leukotrienes receptor antagonist which blocks leukotriene-D4-induced bronchoconstriction that is primarily used as an FDA-approved asthma-controller drug, exercise-induced bronchoconstriction prophylaxis, and for treatment of allergic rhinitis.[6] Of note, not only it does have an inhibitory effect on bradykinin-induced airway hypersensitivity that is the downstream molecule of angiotensin-converting enzyme 2, but also it modulates inflammatory cytokines through the inhibition of NF-κB activation.[18] Moreover, the beneficial anti-viral activity of montelukast against Middle-East respiratory syndrome coronavirus (MERS-CoV) has been reported recently. Therefore, considering the common ancestral origin of SARS-CoV-2 and MERS-CoV, the same effect of montelukast can be expected in SARS-CoV-2.[19]

Hence, by carefully studying the pathogenesis and clinical signs of patients with SARS-CoV-2, the use of bromelain and montelukast may have a synergic effect on the treatment process of these patients. However, to determine the type of treatment, the amount of administration, the duration of action of the drug, and the possible adverse effects, the implementation of a clinical process can play an effective role.

Materials and Methods

The present double-blind clinical trial study was approved by the Ethics Committee in the Biomedical Research of Masih Daneshvari Hospital (No. IR.SBMU.NRITLD.REC.1399.060) and registered in Iranian Registry of Clinical Trials (https://en.irct.ir/trial/49112). Patients with the novel coronavirus (COVID-19) referred to Masih Daneshvari hospital in Tehran were included in the study if they met the inclusion and exclusion criteria after providing full explanations and obtaining written consent. The inclusion criteria were definitive COVID-19 infection based on clinical and para-clinical tests, 18 years < age < 65 years, and patients admitted to the ward with moderate symptoms.[20] On the other hand, excluded factors included intubated patients, liver and kidney enzymes > 2 times the normal limit, drug allergy, opium or alcohol addiction, and recent corticosteroids consumption. The research physicians were blinded to the patient group, and the patients were blinded to the injected drug (double-blind). Eventually, 40 patients with COVID-19 were included in the study and randomly divided into intervention and placebo groups (Figure 1).

In the intervention group, 200 mg oral bromelain was given to patients every 8 hours, along with one tablet of montelukast 10 mg 1 hour before or after dinner for 5 days. In the placebo group, in addition to the defined standard treatment of Masih Daneshvari hospital for patients with a moderate form of infection caused by SARS-CoV2, placebo capsules were administered at the above intervals. Then, several variables were measured during the study period, including oxygen saturation (SaO_2), body temperature, mean arterial pressure, respiratory rate, heart rate, C-reactive protein (CRP), and erythrocyte sedimentation rate. The other parameters were aspartate aminotransferase, alanine aminotransferase, bilirubin (Bil), blood urea nitrogen, creatinine, white blood cells, lymphocyte, lactate dehydrogenase (LDH), and platelet. The results of the questionnaire design and its completion were analyzed using a *t* test and SPSS 25 software.

Results

A total of 51 participants responded to the survey between 20 August and 20 November 2020, of whom 40 (78.43%), with an average age of 56.3 years cases, who provided complete data on variables, were included in the present analyses. According to the results in Table 1, 23 (57.5%) of all individuals were men and 17 (42.5%) cases were women. Accordingly, 12 (30.0%) patients had a history of hypertension. However, diabetes with 6 (15%) cases, hyperlipidemia with 6 (15.0%), and anemia with 4 (10%) were the next most common underlying diseases.

The evaluation of patients' clinical status (Table 2) at different time intervals between intervention and placebo groups in most indicators demonstrated no significant difference between the groups. However, the study of blood SaO_2 percentage on the fifth day in patients in the intervention group was significantly higher than patients in the placebo group ($P = 0.049$).

The examination of patients' laboratory conditions such as immunological factors, kidney function tests, liver function evaluation indices, and coagulation factors at different time intervals in the intervention and placebo groups indicated significant changes between the two groups (Table 3).

The number of lymphocytes in the patients who received bromelain and montelukast was significantly higher after 72 and 120 hours.

The results represented that the concomitant use of bromelain and montelukast could significantly change inflammatory parameters in patients. Thus, CRP significantly decreased compared to the placebo group (after 120 hours $P = 0.043$, Figure 2). The examination of LDH changes showed that the serum level of this index in the intervention group was associated with a decrease in comparison to the placebo group after 120 hours ($P = 0.0351$, Figure 2).

Discussion

Montelukast can inhibit the NF-κB signaling pathway

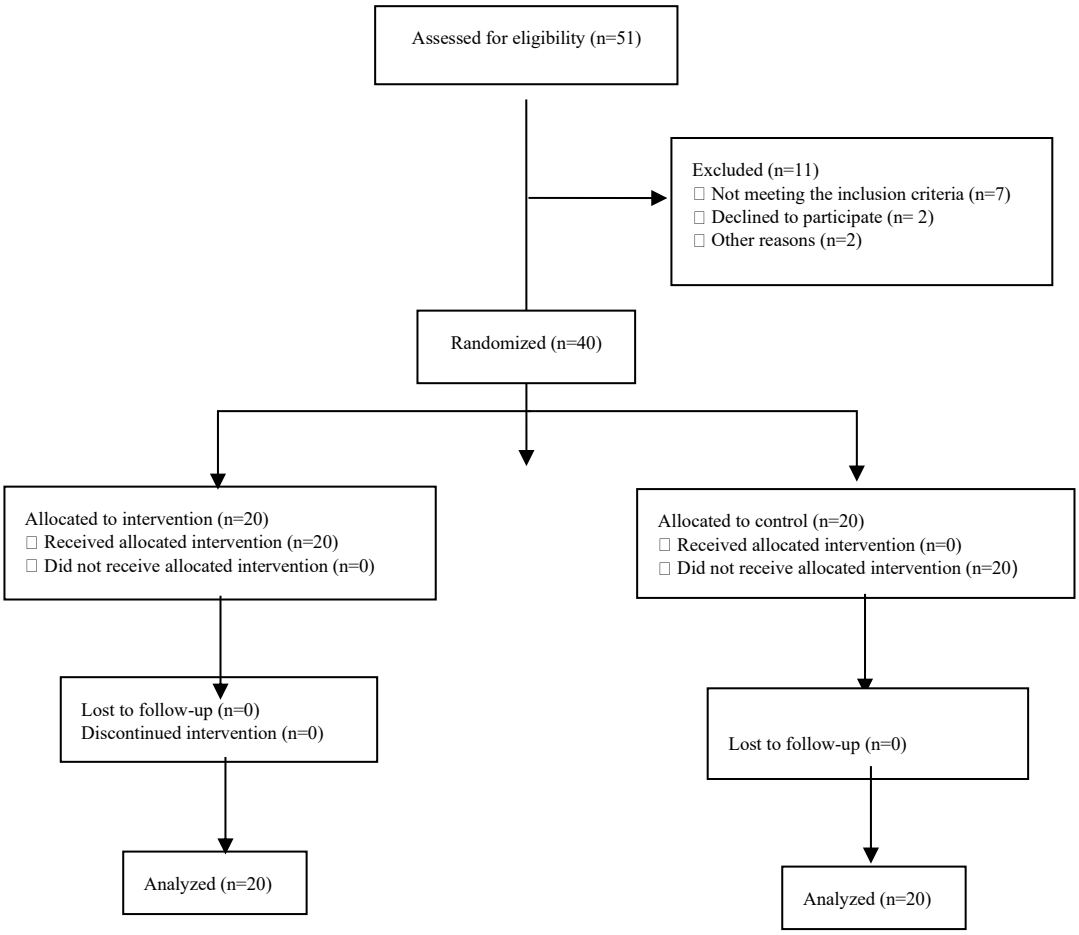

Figure 1. Consort Diagram

Table 1. Demographic Information and Patient Records

Indexes	Mean ± SD	No. (%)
Age	56.3 ± 11.36	-
Gender (male)	-	23 (57.5)
Diabetes	-	6 (15)
HTN	-	12 (30)
CVA	-	1 (2.5)
Kidney disorder	-	3 (7.5)
Liver disorder	-	1 (2.5)
Anemia	-	4 (10)
Hyperlipidemia	-	6 (15.0)
Smoker	-	2 (5)

Note. HTN: Hypertension; CVA: Cerebrovascular accident.

and decrease the release of pro-inflammatory cytokines, which is in agreement with the results of Barré et al, indicating that expressing the role of montelukast in inhibiting COVID-19 serious outcomes.[20-23] Bradykinin is a potent vasoactive mediator that is normally degraded by the ACE. The dysregulated bradykinin signaling is hypothesized to take part in COVID-19 respiratory complications.[24] Given the previous evidence of cysteinyl leukotriene (cysLT) interaction with bradykinin, montelukast was assumed to inhibit bradykinin-induced tracheal smooth muscle contraction in SARS-CoV-2.[25] The related known comorbidities of SARS-CoV-2 encompassing obesity and age were also considered to be manageable with montelukast in the context of COVID-19. Bromelain as a complex natural mixture of cysteine proteinases with the ability to modulate immune responses.[26] It affects the synthesis of prostaglandins by reducing the serum levels and tissues of quinogen and bradykinin and thus manifests its anti-inflammatory effects.[27] It has previously been found that specific proteolytic removal of CD128 molecules by bromelain inhibits the migration of neutrophils to IL-8 and thus reduces acute responses to inflammatory stimuli.[26] The results suggest that the suppression of signaling pathways by bromelain's proteolytic activity may contribute to the anti-inflammatory activity of bromelain.[28]

The results of our study, examining the effects of bromelain and montelukast on patients with COVID-19, revealed that they could decrease CRP as an important inflammatory indicator compared to the control group in one time period (after 120 hours). A similar result was observed for the LDH index, and it was lower in the bromelain and montelukast groups on the fifth day after

Table 2. Evaluation and Comparison of Clinical Factors of Patients in the Intervention Group Compared to the Placebo Group

		Intervention Group	Placebo Group	*P* Value
SaO_2	Before	91.0±29.3	89.9±5.3	0.758
	After 24 hours	92.1±34.5	87.8±31.1	0.052
	After 72 hours	95.3±20.5	93.8±39.1	0.058
	After 120 hours	97.1±43.5	88.2±41.2	0.049
Temp	Before	37.7±18.0	37.3±18.1	0.182
	After 24 hours	37.4±15.5	37.2±17.5	0.643
	After 72 hours	37.7±18.3	37.4±18.5	0.317
	After 120 hours	37.7±11.6	37.0±18.5	0.005
MAP	Before	76.1±45.9	106.9±52.4	0.108
	After 24 hours	109.3±51.2	111.6±52.4	0.058
	After 72 hours	104.1±25.1	103.5±52.7	0.073
	After 120 hours	104.4±22.9	105.1±54.9	0.313
RR	Before	16.6±8.2	22.2±11.0	0.140
	After 24 hours	18.8±8.6	22.6±11.5	0.460
	After 72 hours	18.6±6.8	20.4±11.0	0.767
	After 120 hours	17.7±6.4	21.1±10.4	0.195
HR	Before	87.1±35.8	88.1±24.0	0.432
	After 24 hours	81.3±37.8	83.5±32.5	0.513
	After 72 hours	82.5±42.6	87.5±37.1	0.106
	After 120 hours	82.2±38.4	83.0±31.4	0.218

Note. SaO_2: Oxygen saturation; Temp: Temperature; MAP: Mean arterial pressure; RR: Respiratory rate; HR: Heart rate.

the initiation of the drug.

Based on their immune-modulatory characteristics, bromelain and montelukast can modify immunological responses in patients such as those with COVID-19 who present with the manifestations of lymphocytosis and leukopenia.[29] According to the results obtained in our study, this effect of bromelain and montelukast was observed so that patients in the sample group had higher lymphocytes, thus we are in a better situation in this view between 72 and 120 hours after drug consumption. We have previously shown that the use of bromelain can reduce inflammation in patients with COVID-19.[30]

It has previously been shown that the use of bromelain in animal models reduces airway reactivity, thereby improving the state of saturated oxygen (SaO_2) in the sample population.[23] These effects are due to reduced sensitivity to stimuli, pneumonia markers, and modulation of local airway safety aspects.[24,25] However, the results of other studies confirmed the positive effect of montelukast on the respiratory condition of patients with asthma and could reduce cough in patients with pneumonia.[31-33] Accordingly, in our results, the intake of bromelain and montelukast caused a significant increase in SaO_2 levels compared to the control group in patients with COVID-19 on the fifth day of treatment. The findings of a previous study demonstrated the positive effect of bromelain use on increasing SaO_2.[30]

Table 3. Evaluation and Comparison of Laboratory Indexes of Patients in the Intervention Group Compared to the Placebo Group

		Intervention Group	Placebo Group	*P* Value
WBC (×1000)	Before	1809.3±3810.2	2721.6±4434.6	0.316
	After 24 hours	4472.2±3532.5	4826.8±4506.1	0.167
	After 72 hours	4190.8±3767.9	6128.1±6039.0	0.075
	After 120 hours	5615.6±3435.6	6620.2±7360.1	0.056
Lymph (10^9/L)	Before	0.9±0.4	0.87±0.51	0.187
	After 24 hours	0.96±0.69	0.88±.56	0.074
	After 72 hours	1.09±0.59	0.91±0.62	0.041
	After 120 hours	1.06±0.62	0.90±0.54	0.042
BUN	Before	39.5±22.2	48.0±34.0	0.095
	After 24 hours	46.1±27.1	77.3±75.0	0.062
	After 72 hours	47.8±13.6	72.8±66.1	0.017
	After 120 hours	49.3±14.2	70±54.6	0.093
Cr	Before	1.4±0.7	1.2±0.3	0.576
	After 24 hours	1.4±0.8	1.6±1.1	0.146
	After 72 hours	1.5±0.6	1.4±1.0	0.091
	After 120 hours	1.4±0.77	1.2±0.7	0.073
ALT	Before	37.8±17.1	64.0±29.7	0.192
	After 24 hours	32.9±17.0	98.6±70.9	0.106
	After 72 hours	60.2±19.5	89.1±71.1	0.068
	After 120 hours	63.171±18.2451	82.2451±60.124	0.071
AST	Before	39.0±16.8	67.4±37.7	0.272
	After 24 hours	27.0±13.1	90.1±42.6	0.098
	After 72 hours	58.2±18.5	59.7±34.4	0.324
	After 120 hours	59.1±18.1	60.5±35.2	0.098
Bili	Before	0.736±0.346	0.771±0.458	0.069
	After 24 hours	0.64±0.29	0.96±0.55	0.027
	After 72 hours	0.725±0.319	0.8±0.458	0.138
	After 120 hours	0.9±0.500	0.641±0.361	0.374
Plt	Before	160057±497789	80752±138242	0.313
	After 24 hours	95391±84909	114235±2276813	0.144
	After 72 hours	82284±83489	124862±144469	0.088
	After 120 hours	125075±66425	119437±150733	0.058

Note. WBC: Withe blood cells; BUN: Blood urea nitrogen; Cr: Creatinine; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Bili: Bilirubin; Plt: Platelet.

Our study had limitations such as a small sample size, lack of extensive measurement of immunological factors (e.g., interleukins and cytokines), and lack of measurement of further coagulation factors (e.g., prothrombin time and partial thromboplastin time). Meanwhile, due to the severity of the new coronavirus outbreak, it was difficult to increase the sample size in the initial study. On the other hand, due to various

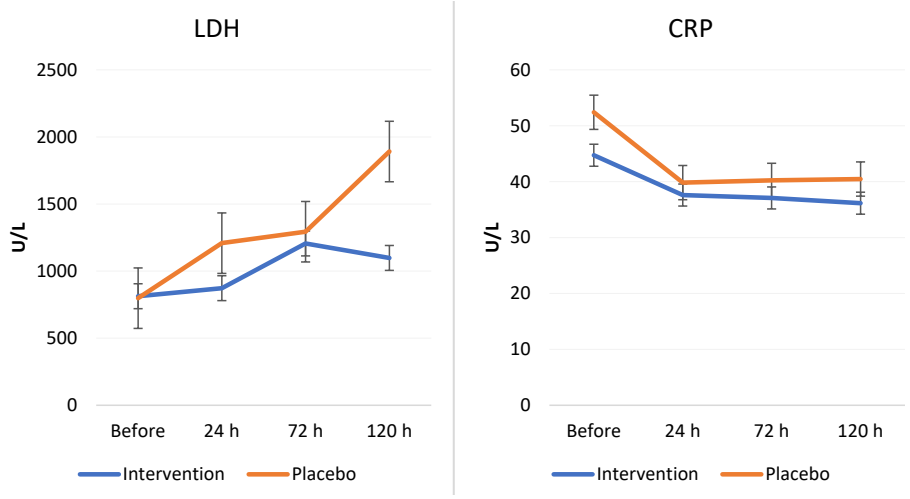

Figure 2. Comparison of the Course of Changes in Inflammatory Factors in Patients in the Intervention Groups Compared to Placebo Group Patients at Different Times. Note. *CRP: C-reactive protein*; LDH: Lactate dehydrogenase

limitations, it was impossible to measure immunological and coagulation tests extensively.

Conclusion

The results of the present study demonstrated that the use of bromelain and montelukast can improve the clinical and para-clinical condition of hospitalized COVID-19 patients with moderate symptoms by the positive effect on lymphocytes, serum levels of CRP, LDH, and SaO_2.

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Authors' Contribution

Conceptualization: Alireza Jahangirifard.
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Funding acquisition: Alireza Jahangirifard.
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Supervision: Kamal Fani.
Validation: Kamal Fani.
Visualization: Kamal Fani.
Writing–original draft: Seyed Bashir Mirtajani.
Writing–review & editing: Seyed Bashir Mirtajani & Alireza Jahangirifard.

Competing Interests

None.

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