The Effect of Bromelain (Anaheal) on Clinical and Para-Clinical Parameters in Hospitalized COVID-19 Patients

Alireza Jahangirifard[1], Ashkan Omidi[2], Kurdistan Sharifzadeh[3], Seyed Bashir Mirtajani[1], Farzad Peyravian[4], Saeid Safari[5], Maedeh Sadat Jafarzadeh[6], Seyed Hadi Mirhashemi[7], Behrooz Farzanegan[6]

[1] *Lung Transplant Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2] *School of Medicine, Tehran Medical Branch, Islamic Azad University, Tehran, Iran*

[3] *Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[4] *School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[5] *Functional Neurosurgery Research Center, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[6] *Critical Care Quality Improvement Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[7] *Department of General Surgery, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Received: 14 Apr. 2021; Accepted: 16 Nov. 2021

Abstract- The severity of COVID-19 disease and its mortality may be due to a localized vascular problem owing to the activation of bradykinin B1 receptors on endothelial cells in the lungs that occur following inflammation. Bromelain acts as an anti-inflammatory factor and can lower the level of bradykinin in the serum and tissues. 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. The 40 patients with mild to moderate symptoms were randomly divided into the control group (No: 20) and sample (No: 20). In the sample group, a dose of 200 mg bromelain was given to patients every 8 hours. In the control group, placebo capsules were administered exactly at the above intervals. Clinical and paraclinical factors (including SaO2, RR body temperature, MAP, HR, CRP, ESR, AST, ALT, Bil, BUN, Cr, WBC, Lymph, LDH, Plt were evaluated on a regular basis for up to five days. The results were evaluated using t-test and SPSS21 software. After treatment, the sample (Bromelain) group indicated significant improvement in SaO2, RR, HR, AST, ALT, BUN, ESR, LDH, and WBC and Lymphocyte count (P<0.05). Other factors did not have a significant difference with the control group. Bromelain causes improvement in some clinical symptoms such as respiratory parameters and para clinical items of mild to moderate hospitalized COVID-19 patients, so it can be a promising treatment. Furthered evaluation of larger groups is recommended.

Acta Med Iran 2021;59(12):726-732.

Keywords: Bromelain; Coronavirus disease 2019 (COVID-19); Inflammatory response; Clinical symptoms; Respiratory parameters; Immunological factors

Introduction

Undoubtedly, the biggest challenge of the last year in all countries of the world is to deal with the outbreak of the novel coronavirus (SARS-COV-2), which was spread from Wuhan, China, to other parts of the world at the end of 2019 (1-3).

COVID-19 infection causes localized pulmonary angioedema, which is accompanied by an increase in the influx of local immune cells and proinflammatory cytokines (4,5). This inflammation persuades more B1 expression, and possibly via antibody-dependent increase of viral infection leading to continued ACE2 dysfunction in the lung because of the durability of the virus (6). From

Corresponding Author: B. Farzanegan
Critical Care Quality Improvement Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 2127122537, Fax: +98 2126109644, E-mail address: farzaneganbehrooz@gmail.com

this standpoint, bradykinin-dependent local lung angioedema via B1 and B2 receptors is a significant trait of SARS-COV-2 (7).

Bradykinin B1 and B2 receptors are constitutively expressed in the airways on several residential and/or immune cells (8,9). Their expression can also be induced by inflammatory mediators, usually associated with eosinophil and neutrophil recruitment, such as IL-4, IL-13, TNF-α, IL-6, and IL-8, via intracellular MAPK and NF-κB signaling (10). BK exerts its pharmacological effects, mainly vasodilation, by activating constitutively expressed B2 receptors (11).

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

Bromelain is an anti-inflammatory that plays a role in reducing serum and tissue levels of kininogen and bradykinin (14). This substance is obtained from raw pineapple extract, and if orally administered while retaining its properties, it is reabsorbed through the intestines (15). Numerous therapeutic properties of this substance are known for many diseases, including bronchitis, sinusitis, arthritis, and inflammation. The positive effects on the mentioned diseases can be attributed to the anti-edema, anti-inflammatory, and coagulation-inhibiting properties of bromelain (16). These effects are due to an enhancement of the serum fibrinolytic activity and inhibition of the fibrinogen synthesis, as well as a direct degradation of fibrin and fibrinogen (13). As mentioned, bromelain has anti-inflammatory properties. On the other hand, this drug potentially activates the immune system in association with the rapid response to cellular stress (17). Conversely, bromelain reduces cytokines secretion when immune cells are already stimulated in the condition of inflammation-induced overproduction of cytokines.

Thus, by carefully studying the pathogenesis and clinical signs of patients with SARS -COV-2, the use of Bromelain can have a positive effect on the treatment process of these patients. However, in order to determine the type of treatment, the amount of administration, the duration of action of the drug, and to determine the possible adverse effects, the implementation of a clinical process can play an effective role.

Materials and Methods

This study, which is designed as a double-blind clinical trial (with registration number: IRCT20150725023332N3), has been approved by the Ethics Committee in Biomedical Research of Masih Daneshvari Hospital with the code (IR.SBMU.NRITLD.REC.1399.060). Patients with the novel coronavirus (COVID-19) referred to Masih Daneshvari Hospital in Tehran were included in the study if they met the inclusion criteria (Definitive COVID-19 infection based on clinical and Para clinical tests, 18 years<Age<65 year and patients admitted to the ward with mild to moderate symptoms) and Excluded factors (Intubated, liver and kidney enzymes> 2 times the normal limit, drug allergy, opium addiction, alcohol addiction and patients who have recently used corticosteroids) and after providing full explanations and obtaining written consent. The research physicians were blinded to the patient group, and the patients were blinded to the injected drug (double-blind). Forty patients with the new coronavirus (COVID-19) were included in the study. Patients were then randomly divided into two groups: sample and control (Figure 1).

In the sample group, a dose of 200 mg oral bromelain (Anaheal brand from SPAmeda) was given to patients every 8 hours for five days. In the control group, placebo capsules were administered exactly at the above intervals. Then variables such as Oxygen saturation (SaO2), Body Temperature (Temp), Mean Arterial Pressure (MAP), Respiratory Rate (RR), Heart Rate (HR), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Bilirubin (Bil), blood urea nitrogen (BUN), Creatinine (Cr), Withe blood cells (WBC), Lymphocyte, Lactate dehydrogenase (LDH), Platelet (Plt), were measured during the study period. The results of questionnaire design and its completion were analyzed using t-test and SPSS25 software.

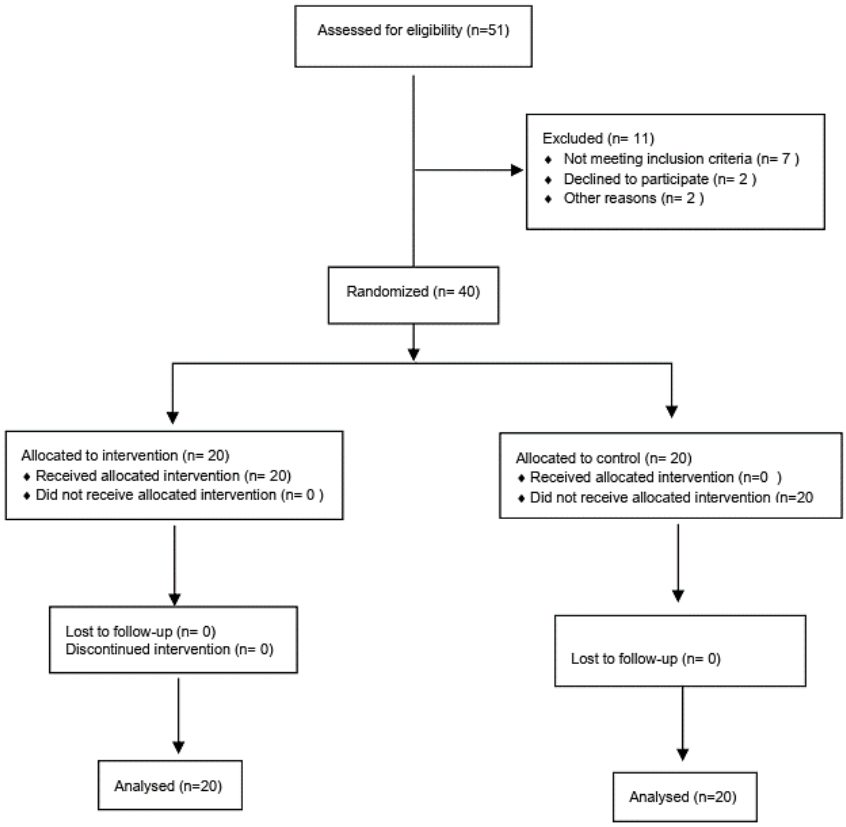

Figure 1. Consort diagram

Results

A total of 51 participants responded to the survey between 20 April and 20 June 2020, of whom 40 (78.43%) with an average age of 58.4 years, provided complete data on variables included in the present analyses. According to the results in Table 1, 21 (52.5%) of all individuals were men and 19 (47.52%) were women. Accordingly, 10 (24.4%) patients had a history of hypertension. However, diabetes with 6 (15%) cases, hyperlipidemia with 5 (12.5 %), and Anemia with 4 (10%) were the next most common underlying diseases.

Evaluation of patients' clinical condition (Table 2) at different time intervals between the sample and control groups in some indicators (Sao2, Temp, MAP, RR, HR) showed a significant difference between the groups.

Meanwhile, the numerical amount of SaO2 in patients in the bromelain group increased significantly at 72 and 120 hours after treatment. However, based on the results in the relevant periods, we saw a decrease in RR in patients receiving bromelain.

Examination of MAP index shows that although its numerical value was lower in the sample group than the control group, these values were always in the normal range. However, the heart rate among patients in the bromelain group was lower than the other group, and it was significant after 72 hours.

Examination of patients' laboratory conditions such as Immunological factors (WBC, Lymph), kidney function tests (BUN and Cr), liver function evaluation indices (AST, ALT), and coagulation factors (Plt and INR) at different time intervals in the sample and control groups showed significant changes between the two groups (Table 3).

Accordingly, the white blood cells count in the sample group (at 72 hours and 120 hours) was significantly better than the other group. Also, the number of lymphocytes in the patients who received bromelain was significantly higher during the mentioned period.

On the other hand, our results showed that the patients in the sample group had lower levels of BUN, AST, and ALT in comparison to the control one. These changes became significant over time (after the third day of treatment).

The results in Figure 2 show that the use of Bromelain could significantly change the inflammatory parameters

in patients. Thus, ESR decreased compared to the control group (after 24 hours: *P*=0.04862 AND after 120 hours *P*=0.0259), while serum CRP levels did not differ significantly between the two groups (*P*>0.05). Examination of LDH changes showed that the serum level of this index in the sample group was associated with a decrease compared to the control group after 24 hours and 120 hours.

Table 1. Demographic information and patient records

Indexes	Mean	N (%)
Age	**58.4**	–
Sex (male)	–	**21** (**52.5**%)
Diabetes	–	**6** (**15**%)
HTN	–	**10** (**25**%)
MI	–	**0** (**0**%)
CVA	–	**1** (**2.5**%)
Kidney disorder	–	**3** (**7.5**%)
Liver disorder	–	**1** (**2.5**%)
Anemia	–	**4** (**10**%)
Hyperlipidemia	–	**5** (**12.5**%)
Smoker	–	**2** (**5**%)
Opium	–	**0** (**0**%)

Table 2. Evaluation and comparison of clinical factors of patients in the intervention group (sample group) compared to the control group

		Sample group	Control group	*P*
Sao2	**Before**	92/625± 29/3958	89/94444± 5/359024	0/65825
	After 24 h	86/854± 31/1456	92/13333± 34/55681	0/0724
	After 72 h	98/3± 20/5086	93/85714± 39/16773	0/04872
	After 120 h	95/15385± 42/69	82/0± 0/259077	0/04052
Temp	**Before**	37/42± 18/02122	37/3± 18/18948	0/192
	After 24 h	37/39± 16/552	37/27± 17/57	0/543
	After 72 h	37/841± 18/3185	37/4± 18/59	0/107
	After 120 h	37/1± 11/65945	37/01± 18/50	0/0052
MAP	**Before**	75/55± 45/90333	106/9167± 52/46142	0/048
	After 24 h	104/342± 51/28	111/6154± 52/40774	0/018
	After 72 h	100/1± 25/1968	103/5± 52/75862	0/023
	After 120 h	100± 22/90614	105/1± 54/99812	0/213
RR	**Before**	15/6047± 8/2308	22/26667± 11/09666	0/131
	After 24 h	18/8287± 8/6762	22/69231± 11/50429	0/460
	After 72 h	12/4162± 6/8919	20/45455± 11/00631	0/0167
	After 120 h	12/72± 6/4254	21/142564± 10/4587	0/0195
HR	**Before**	85± 35/83019	88/17647± 24/05504	0/232
	After 24 h	80/332± 37/891	83/53333± 32/59199	0/413
	After 72 h	76/5125± 42/648	87/57143± 37/10629	0/008
	After 120 h	80/25± 38/4899	83± 31/47883	0/001

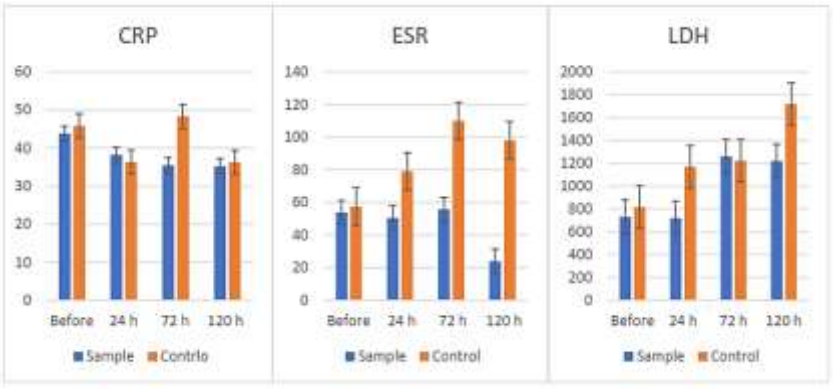

Figure 2. Comparison of the level of changes in inflammatory factors in patients in the intervention groups (sample group) compared to control group patients at different times

Table 3. Evaluation and comparison of laboratory indexes of patients in the intervention group (sample group) compared to the control group

		Sample group	Control group	*P*
WBC ×1000	**Before**	1689/3± 3810/22	2721/67± 4434/687	0/2162
	After 24 h	4222/26± 3532/5	4826/874± 4506/131	0/1372
	After 72 h	3790/8± 3767/91	6128/171± 6039/098	0/0556
	After 120 h	5005/62± 3435/6	6620/25± 7360/129	0/0265
Lymph (10^9 /L)	**Before**	0/91 ± 0/44	0/87± 0/51	0/190
	After 24 h	0/93± 0/69	0/88± /56	0/084
	After 72 h	1/09± 0/59	0/91± 0/62	0/043
	After 120 h	1/07± 0/62	0/90± 0/54	0/047
BUN	**Before**	36/5625± 22/272	48± 34/05877	0/035
	After 24 h	46± 27/14365	77/36364± 75/06723	0/05407
	After 72 h	43/5± 13/67175	72/81818± 66/1843	0/01050
	After 120 h	41/5± 13/22094	70± 54/67784	0/002
Cr	**Before**	1/35882± 0/727	1/272222± 0/337977	0/477
	After 24 h	1/32125± 0/8068	1/6± 1/188629	0/135
	After 72 h	1/4± 0/683852	1/4± 1/05935	0/0419
	After 120 h	1/6± 0/772602	1/276923± 0/794114	0/021
ALT	**Before**	30/4709± 17/106	64/012± 29/761	0/1441
	After 24 h	30/8± 17/08223	98/637± 70/9021	0/2058
	After 72 h	62± 19/51036	89/125± 71/18843	0/0381
	After 120 h	60/124± 18/2451	82/2451± 60/124	0/0315
AST	**Before**	38/885± 16/854	67/4± 37/754	0/261754
	After 24 h	26/8± 13/14544	90/18182± 42/6751	0/060731
	After 72 h	59± 18/54491	59/75± 34/45161	0/021257
	After 120 h	57/24± 18/1245	60/54± 35/2431	0/03012
Bili	**Before**	0/63636± 0/3463	0/771429± 0/458258	0/0694
	After 24 h	0/64± 0/299176	0/966667± 0/557026	0/0271
	After 72 h	0/725± 0/319963	0/8± 0/45812	0/1380
	After 120 h	0.9 ± 0.500	0.641± 0.361	0.374
Plt	**Before**	160057± 497789	80752/06± 138242	0/313295
	After 24 h	95391± 84909/8	114235/6± 2276813	0/144134
	After 72 h	82284 ± 83489	124862/7± 144469/1	0/088424
	After 120 h	145075± 66425/8	119437± 150733/6	0/04407
INR	**Before**	1/2506± 0/4046	1/260588±0/153564	0/088064
	After 24 h	1/2571± 0/62127	1/187273± 0/592923	0/131902
	After 72 h	1/261818± 0/632551	1/2025± 0/50233	0/007326
	After 120 h	1/331818± 0/665592	1/075± 0/338764	0/00026

Discussion

Bromelain is a complex natural mixture of cysteine proteinases with the ability to modulate immune responses (18). It affects the synthesis of prostaglandins by reducing serum levels and tissues of quinogen and bradykinin and thus manifests its anti-inflammatory effects (19). It has previously been shown 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 (18). The results suggest that the suppression of signaling pathways by bromelain's proteolytic activity may contribute to the anti-inflammatory activity of bromelain (20).

The results of our study, which examined the effects of bromelain on patients with COVID-19, showed that although bromelain did not significantly change serum CRP levels, but could decrease ESR as an important inflammatory indicator compared to the control group in three time periods (24 hours, 72 hours and 120 hours). A similar result was observed for the LDH index, and it was lower in the bromelain group during the first day after initiation of the drug and also on the fifth day.

Based on immune-modulatory characteristics of the bromelain, it can modify immunological responses in patients such as those with COVID-19 who present with manifestations of lymphocytosis and leukopenia (21). According to the results obtained in our study, this effect of bromelain was observed so that the patients in the sample group had lower WBC counts and higher lymphocytes, so they were in a better situation in this view between 72 hours and 120 hours after drug consumption.

In a murine model of acute asthma, bromelain decreased airway reactivity and improved the state of saturated oxygen (SaO2) in the sample population (22). These effects are due to the reduction of airway response and sensitivity to irritants, the reduction of markers of pneumonia, and the modulation of safety aspects of local airways following the use of bromelain (23,24). Our results also indicate the positive effect of bromelain use. Accordingly, bromelain intake caused a significant increase in SaO2 levels compared to the control group in patients with COVID-19. Besides bromelain role in reducing the airway reactivity and inflammatory response, which can be in charge of improving pulmonary function, anticoagulant effects of this substance may be another reason for modifying the respiratory system because it is clarified that micro thrombosis can deteriorate the lung function during the COVID-19 disease second phase (25).

Facts and figures show that patients in the study group had a lower heart rate in a minute which can be important because almost the aged population in the study may be at greater risk of cardiac diseases, especially while having comorbidity diseases such as diabetes mellitus and hypertension. This may be due to a higher level of oxygen in the blood and better pulmonary function that decrease the heart load and allows work to be more comfortable.

Another considerable result was a significant decrease in serum levels of AST and ALT ($P<0.05$) as factors evaluating liver function in patients with COVID-19 in this study. The results of Al-Otaibi *et al*., Showed that Co-administration of stem bromelain with lead markedly reduced the lead accumulation in the kidney and spleen (26). The lead-induced modulated levels of serum ALT and AST were also alleviated by bromelain treatment.

The lower level of serum BUN among patients in the sample group in the present study was consistent with the results of research by Nguyen *et al*., (2018) and Hossain *et al*., (2015) (27,28). Accordingly, consumption of bromelain in treated pigs reduced serum BUN levels.

These great results in the organ functions after using Bromelain in the patients suffering from SARS-COV2 can be foresighted regarding anti-inflammatory mechanisms of the mentioned drug and can be promising in the treatment of these patients (3).

Bromelain has some anti-coagulation characteristics and is expected to impress the coagulation state in the patients (29); however, this study signified that INR was remarkably lower in the sample group only on the day fifth and two groups were in the same situation in the other times. This is an excellent result and indicates that the COVID patients might have a better medical condition if they receive the drug for a longer period and maybe in a larger amount.

Our study had limitations such as small sample size, lack of extensive measurement of immunological factors (such as interleukins and cytokines), and lack of measurement of further coagulation factors (such as PT, PTT). 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 limitations, it was not possible to measure immunological and coagulation tests extensively.

The results of the present study showed that the use of bromelain could improve the clinical condition of mild to moderate hospitalized COVID-19 patients by increasing the percentage of blood oxygen saturation, decreasing RR and HR. However, the positive effect of bromelain on lymphocytes and leukocytes count, serum levels of liver function indices (AST and ALT), and renal function test (BUN) have also been considered in improving the condition of patients.

Acknowledgments

The authors express their sincere thanks to the staff of Masih Daneshvari Hospital, Tehran, Iran, for their assistance.

References

1. Abedini A, Mirtajani SB, Karimzadeh M, Jahangirifard A, Kiani A. Can Hesperidin be the Key to the Treatment of Severe Acute Respiratory Syndrome COV-2? Biomed Biotechnol Res J 2020;4:108-9.
2. Lau H, Khosrawipour V, Kocbach P, Mikolajczyk A, Schubert J, Bania J, et al. The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China. J Travel Med 2020;27:taaa037.
3. Marjani M, Tabarsi P, Moniri A, Hashemian SM, Nadji SA, Abtahian Z, et al. NRITLD Protocol for the Management of Patients with COVID-19 Admitted to Hospitals. Tanaffos 2020;19:91-9.
4. Manolis AS, Manolis TA, Manolis AA, Melita H. The Controversy of Renin–Angiotensin-System Blocker Facilitation Versus Countering COVID-19 Infection. J Cardiovasc Pharmacol 2020;76:397-406.
5. Polycarpou A, Howard M, Farrar CA, Greenlaw R, Fanelli G, Wallis R, et al. Rationale for targeting complement in COVID-19. EMBO Mol Med 2020;12:e12642.
6. Sharifzadeh K, Farzanegan B, Mirtajani SB, Peyravian F, Jahangirifard A. The Potential Role of Bromelain in the

Treatment of SARS-COV-2. J Cell Mol Anesth 2018;5:284-5.
7. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med 2020;288:192-206.
8. Ricciardolo FL, Folkerts G, Folino A, Mognetti B. Bradykinin in asthma: Modulation of airway inflammation and remodelling. Eur J Pharmacol 2018;827:181-8.
9. Dutra RC, Bento AF, Leite DF, Manjavachi MN, Marcon R, Bicca MA, et al. The role of kinin B1 and B2 receptors in the persistent pain induced by experimental autoimmune encephalomyelitis (EAE) in mice: evidence for the involvement of astrocytes. Neurobiol Dis 2013;54:82-93.
10. Vo TS, Ngo DH, Kim SK. Potential targets for anti-inflammatory and anti-allergic activities of marine algae: An overview. Inflamm Allergy Drug Targets 2012;11:90-101.
11. Prado GN, Taylor L, Zhou X, Ricupero D, Mierke DF, Polgar P. Mechanisms regulating the expression, self-maintenance, and signaling-function of the bradykinin B2 and B1 receptors. J Cell Physiol 2002;193:275-86.
12. Prins M, Schellens CJ, Van Leeuwen MW, Rothuizen J, Teske E. Coagulation disorders in dogs with hepatic disease. Vet J 2010;185:163-8.
13. Zhai Z, Li C, Chen Y, Gerotziafas G, Zhang Z, Wan J,et al. Prevention and treatment of venous thromboembolism associated with coronavirus disease 2019 infection: a consensus statement before guidelines. Thromb Haemost 2020;120:937-48.
14. Seligman B. Bromelain: an anti-inflammatory agent. Angiology 1962;13:508-10.
15. Hale LP, Greer PK, Trinh CT, James CL. Proteinase activity and stability of natural bromelain preparations. Int Immunopharmacol 2005;5:783-93.
16. Moghadam MY, Nemat-Shahi M, Dowlat-Abadi B, Safari SE, Yajan S. Association Between Bispectral Index (BIS) Value and Postoperative Shivering in Patients Undergoing Orthopedic Surgery. Open Access Maced J Med Sci 2019;7:1166-9.
17. Engwerda CR, Andrew D, Ladhams A, Mynott TL. Bromelain modulates T cell and B cell immune responses in vitro and in vivo. Cell Immunol 2001;210:66-75.
18. Salas CE, Gomes MT, Hernandez M, Lopes MT. Plant cysteine proteinases: evaluation of the pharmacological activity. Phytochemistry 2008;69:2263-9.
19. Metzig CA, Grabowska ED, Eckert KL, Rehse KL, Maurer HR. Bromelain proteases reduce human platelet aggregation in vitro, adhesion to bovine endothelial cells and thrombus formation in rat vessels in vivo. In vivo. 1999;13:7-12.
20. Huang JR, Wu CC, Hou RC, Jeng KC. Bromelain inhibits lipopolysaccharide-induced cytokine production in human THP-1 monocytes via the removal of CD14. Immunol Invest 2008;37:263-77.
21. Ahmed AK, Albalawi YS, Shora HA, Abdelseed HK, Al-Kattan AN. Effects of quadruple therapy: zinc, quercetin, bromelain and vitamin C on the clinical outcomes of patients infected with COVID-19. Rea Int J End Diabet 2020;1:18-21.
22. Secor Jr ER, Carson IV WF, Cloutier MM, Guernsey LA, Schramm CM, Wu CA, Thrall RS. Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease. Cell Immunol 2005;237:68-75.
23. Secor Jr ER, Shah SJ, Guernsey LA, Schramm CM. Bromelain limits airway inflammation in an ovalbumin-induced murine model of established asthma. Altern Ther Health Med 2012;18:9-17.
24. Secor ER, Carson WF, Singh A, Pensa M, Guernsey LA, Schramm CM, et al. Oral bromelain attenuates inflammation in an ovalbumin-induced murine model of asthma. Evid Based Complement Alternat Med 2008;5:61-9.
25. Sagar S, Rathinavel AK, Lutz WE, Struble LR, Khurana S, Schnaubelt AT, et al. Bromelain Inhibits SARS-CoV-2 Infection in VeroE6 Cells. Biorxiv 2020
26. Al-Otaibi WR, Virk P, Elobeid M. Ameliorative potential of stem bromelain on lead-induced toxicity in Wistar rats. Acta Biol Hung 2015;66:149-60.
27. Nguyen DH, Lee SI, Cheong JY, Kim IH. Influence of low-protein diets and protease and bromelain supplementation on growth performance, nutrient digestibility, blood urine nitrogen, creatinine, and faecal noxious gas in growing–finishing pigs. Can J Anim Sci 2018;98:488-97.
28. Hossain MM, Lee SI, Kim IH. Effects of bromelain supplementation on growth performance, nutrient digestibility, blood profiles, faecal microbial shedding, faecal score and faecal noxious gas emission in weanling pigs. Veterinarni Medicina 2015;60:544-52.
29. Hu PA, Chen CH, Guo BC, Kou YR, Lee TS. Bromelain Confers Protection against the Non-Alcoholic Fatty Liver Disease in Male C57bl/6 Mice. Nutrients 2020;12:1458.