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Original Article

Effect of *Plantago major* on cough severity in acute bronchitis: A double-blind randomized clinical trial

Alireza Naderi [1]
Seyyed Ali Mozaffarpur (MD) [2*]
Hoda Shirafkan (PhD) [3]
Masomeh Bayani (MD) [4]
Zahra Memariani (MD) [2]

1. Student Research Center, Babol University of Medical Sciences, Babol, Iran
2. Traditional Medicine and History of Medical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
3. Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
4. Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

*** Correspondence:**
Seyyed Ali Mozaffarpur, Traditional Medicine and History of Medical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

E-mail: seyyedali1357@gmail.com
Tel: +98 11 32194728-30

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Abstract

Background: Treatments for acute bronchitis is usually a supportive care to relieve upper respiratory symptoms. This study aimed to evaluate the effect of *Plantago major* syrup (PMS) on cough severity in acute bronchitis.

Methods: Patients (20-75 years-old) referred to the clinic of infectious diseases in Ayatollah Rouhani Hospital, Babol, Iran with a complaint of cough and the Bronchitis Severity Scale (BSS) ≥5 entered the study. The patients randomly received PMS or placebo 30 ml/day for 10 days. Patients were visited before treatment and on days 5 and 10 after treatment. The primary outcome was BSS score and secondary outcome was the life quality that was measured by means of the Persian version of the Leicester Cough Questionnaire (LCQ) at the first visit and on the 10th day.

Results: Of the 121 patients diagnosed with acute bronchitis, 80 eligible patients (42.87±11.75 years-old) were randomly divided into PMS and placebo groups. The BSS score in the PMS group after 10 days was significantly lower than that of the placebo group (P=0.001). Frequency of cough (P=0.001), sputum production (P=0.005), and chest wall pain (P=0.008) were significantly lower in the PMS group than in the placebo group. In terms of quality of life, all items, including psychological, physical, and social domains, as well as total scores, were altered significantly in the PMS group compared to placebo. During monitoring of side effects, no significant adverse effects were stated in either group.

Conclusion: The study indicates the palliative effects of PMS in relieving the symptoms of acute bronchitis and improving quality of life.

Keywords: Persian medicine, Plantago major, Complementary therapies, Cough, Herbal.

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Acute bronchitis is a clinical syndrome characterized by a self-limiting inflammatory phase in the large and medium airways. This syndrome generally occurs due to a viral infection and is not related with evidence of pneumonia on chest radiography. This disease occurs mostly in the winter season and its characteristic is mainly starting with a dry/productive cough that usually lasts less than three weeks. These definitions are not related to acute exacerbation of chronic bronchitis; it should also be differentiated from acute bronchiolitis. Cough caused by acute bronchitis is one of the most common reasons for people to see a doctor in all age groups (1, 2).

In the process of treating cough, patients are usually trained to benefit from supportive care for relieving upper respiratory symptoms, such as cough and wheezing. In this regard, various approaches are used to relieve acute cough caused by acute bronchitis, including narcotic antitussives, expectorants, anti-histamines, decongestants, and β2 receptors' agonists. Review of clinical trials has not conclusively determined that they are useful (1).

Usually, there is no need to prescribe antibiotics for most people with acute bronchitis, but there is a possibility of overuse in this situation. Reducing the use of anti-microbial drugs in acute bronchitis is one of the important issues of national and international health care (3). Complementary and alternative medicine therapies might decrease the antibiotics prescription and can help current treatments as an option (4). Using herbal products as a common and old choice for many common health problems can be a good option (5). Persian Medicine (PM) is an ancient medical paradigm with developed principles that seek to treat patients with a holistic and person-centered approach. Based on the Avicenna's book (Ibn Sina) (980–1037), cough occurs in three types: Sudden cough, persistent, and the old cough (6).

Plantago major L. is one of the widely used medicinal plants in PM. The subgenus Plantago has a variety of phytochemical compounds mentioned in different studies, including alkaloids, coumarins, flavonoids, sterol, iridoids, mucilage, polysaccharides, and volatiles oil components (7, 8). Further studies have shown that *P. major* and *P. lanceolata* have antibiotic activity against some Gram-negative/-positive bacteria, as well as fungi (9). It has been used for centuries to treat many ailments, especially those of the digestive, respiratory, and reproductive systems, as well as wound healing and inflammatory diseases (10). Although the therapeutic effects of *P. major* in chronic bronchitis have been documented (11), no study has been conducted on the effect of *P. major* in acute viral bronchitis. This study aimed to examine the effect of *Plantago major* on cough severity in acute bronchitis.

Methods

Study design: This double-blind randomized trial started in August 2020 and ended in January 2022 in the infectious diseases clinic of Ayatollah Rouhani Hospital, Babol University of Medical Sciences (BUMS), Babol, Iran. It was approved by the Ethics Committee of BUMS (IR.MUBABOL.HRI.REC.1398.342) and was also registered on the IRCT by the code: IRCT20200105046009N2. All participants filled up the written consent forms.

Participants:

Inclusion criteria: Patients with the age between 20-75 years old and Bronchitis Severity Scale (BSS) ≥ 5 on the first visit entered the study.

Exclusion criteria: We excluded pregnant or breast-feeding women, people with a history of COPD, asthma, lung cancer, bronchiectasis, pneumonia, cystic fibrosis, pulmonary tuberculosis, liver/renal failure, cardiovascular, neurological, metabolic, or hematologic diseases, psychological disorder, history of alcohol use, or substance abuse, the use of antibiotics, bronchodilators, glucocorticoids or immunosuppressive drugs in the last four weeks before study entry, the use of antitussive or mucolytic drugs in the last week before study, and also participation in another trial in the same time.

Drop out criteria: Intolerance to the intervention or any adverse reaction to the medication (nausea/ vomiting, abdominal pain or diarrhea, urticaria), improper use, or refusal to continue the medication.

Entering the study: Patients who were referred to the clinic of the infectious diseases in Ayatollah Rouhani Hospital with a complaint of cough were considered. After acute bronchitis was confirmed by an infectious disease specialist, then the demographic information of the patient was recorded and she/he entered the study

Intervention: The participants were randomly allocated to the study groups, to receive *P. major* syrup (PMS) or placebo. A standard water extract of *Plantago major* manufactured by Sanabel Daru Co. with batch number of 75643256 was used in this study. A syrup of placebo with the same taste and color as PMS prepared by the same company and pharmacist. Based on Persian Medicine books, and the clinical experiences, the amount of 30 ml/day (10 ml, three times a day) in both groups was used for 10 days.

Primary outcome: The severity of acute bronchitis was the primary outcome.

Secondary outcomes: The quality of life, the frequency of cough, dyspnea, the volume and consistency of sputum, and chest wall pain were secondary outcomes.

Evaluation and Follow-up: Participants were followed-up for 10 days. They were visited before the treatment and on days 5 and 10 after the treatment. Patients (either by themselves or with the help of family members/caregivers) were requested for recording the symptoms such as coughing, dyspnea, chest wall pain, and sputum production on a daily record sheet.

The main variable in this survay was change in the BSS score on days 0, 5, and 10. The BSS is a measure used for the acute bronchitis and is also a valid clinical tool for early diagnosis and the evaluation of the treatment. BSS is the sum of five main symptom scores including cough, sputum, dyspnea, chest pain during coughing, and rales on auscultation. Symptoms are scored on 5-point scales (0: absent, 1: mild, 2: moderate, 3: severe, and 4: very severe). Since acute bronchitis generally includes complaints that are subjective, the BSS score based on the patient's

subjective symptoms correlates reasonably well with actual improvement (12). Quality of life (QOL) was evaluated by means of the Persian version of the Leicester Cough Questionnaire (LCQ) at the first visit and on their 10th day. LCQ is the most valid and specific measure for assessment of QOL in patients with acute cough (13). The LCQ used 19 self-reported items to assess the patient's impact of coughing on QOL over the past two weeks. There are three domains (psychological, physical, and social). Overall scores are from 3 to 21, and the domains' scores are from 1 to 7. A higher score shows a better QOL. We also requested participants to report any adverse effects. Patients were called every three days to inquire about possible adverse effects and also for completing the questionnaires. After 10 days, the finished forms were delivered and inspected. Any omissions or unclear points were resolved with the patient's cooperation.

Sample size: By the first type error of 0.05, and the power of 90%, the sample size was determined as 36 cases in each group. Taking into consideration the probable 10% dropout rate, the final sample size was set at 80 cases.

Randomization and concealment: The randomization of the study was done using permutation blocks of 4 for two groups. The randomized sequence was prepared and coded with random codes. Each container had its own unique code and was provided to the researcher in a blind manner. Unlocking the codes was done after the end of the intervention and data analysis. In case of adverse effects, the related code was opened.

Blinding: Identical containers were filled of the drugs of two groups (PMS and placebo) by the study pharmacist and sent to be encoded. The color, smell, taste and shape were completely the same in both groups.

Statistical methods: The obtained data were analyzed via SPSS V.22 software. Mean ± standard deviation (SD) and frequency (%) were used for the descriptive statistics. Kolmogorov-Smirnov test was used to evaluate the normality of the data. Chi-square and t-tests were used to compare two groups at baseline.

For evaluating the effect of PMS between groups, the "intention to treat" (ITT) analysis, was used. Also, the multiple imputation method (EM algorithm) was applied to impute the missing data. We used the "repeated measure" analysis to examine the trend of outcome changes. Analysis of covariance (ANCOVA) was used to assess the effect of the intervention on the patients' quality of life. The "number needed to treat" (NNT) was calculated according to the transformation of eta square to NNT via an online platform. P-values less than 0.05 were considered significant.

Results

Of the 121 patients diagnosed with acute bronchitis, 80 patients met the eligibility criteria and were divided into two groups randomly. The study flow chart was shown in figure 1. The mean age of patients was 42.87 ± 11.75 years (minimum 20 years, maximum 75 years). Of these, 43 (53.8%) were females. The patients' average body mass index (BMI) was also 27.92 ± 4.43 (minimum 19.59, maximum 41.52). Baseline data showed no significant difference between two groups (p value > 0.05). Details are shown in table 1.

Primary outcome: The severity of acute bronchitis (BSS total score) in the PMS group after 10 days was significantly better than the placebo group (p< 0.001, partial eta square = 0.221). The details are shown in table 2.

Table 1. Baseline data of the study participants

		PMS (n=40)	Placebo (n=40)	P-value
Age (years± SD)		43.8±13.38	41.95±9.96	0.485
Sex	**Male**	18	19	0.823
	Female	22	21	
BMI		28.44±4.11	27.42±4.70	0.324
QOL		54.89±10.35	56.22±10.40	0.514
BSS		8.89±2.23	9.46±1.64	0.217

*PMS: Plantago major syrup; BMI: body mass index; QOL: quality of life; BSS: Bronchitis Severity Scale

Secondary outcomes: Frequency of cough (P= 0.001), sputum production (P = 0.005), and chest wall pain (P=0.008) were significantly lower in the PMS group than in the placebo group. Although the severity of dyspnea and rales (in physical examination), was not statistically different between the groups. In terms of QOL, all items,

including physical, psychological, and social domains, as well as total scores, exhibited significant differences in the PMS group in comparison with the placebo. Details are represented in tables 2 and 3. During monitoring of side effects, no significant side effects were stated in either group.

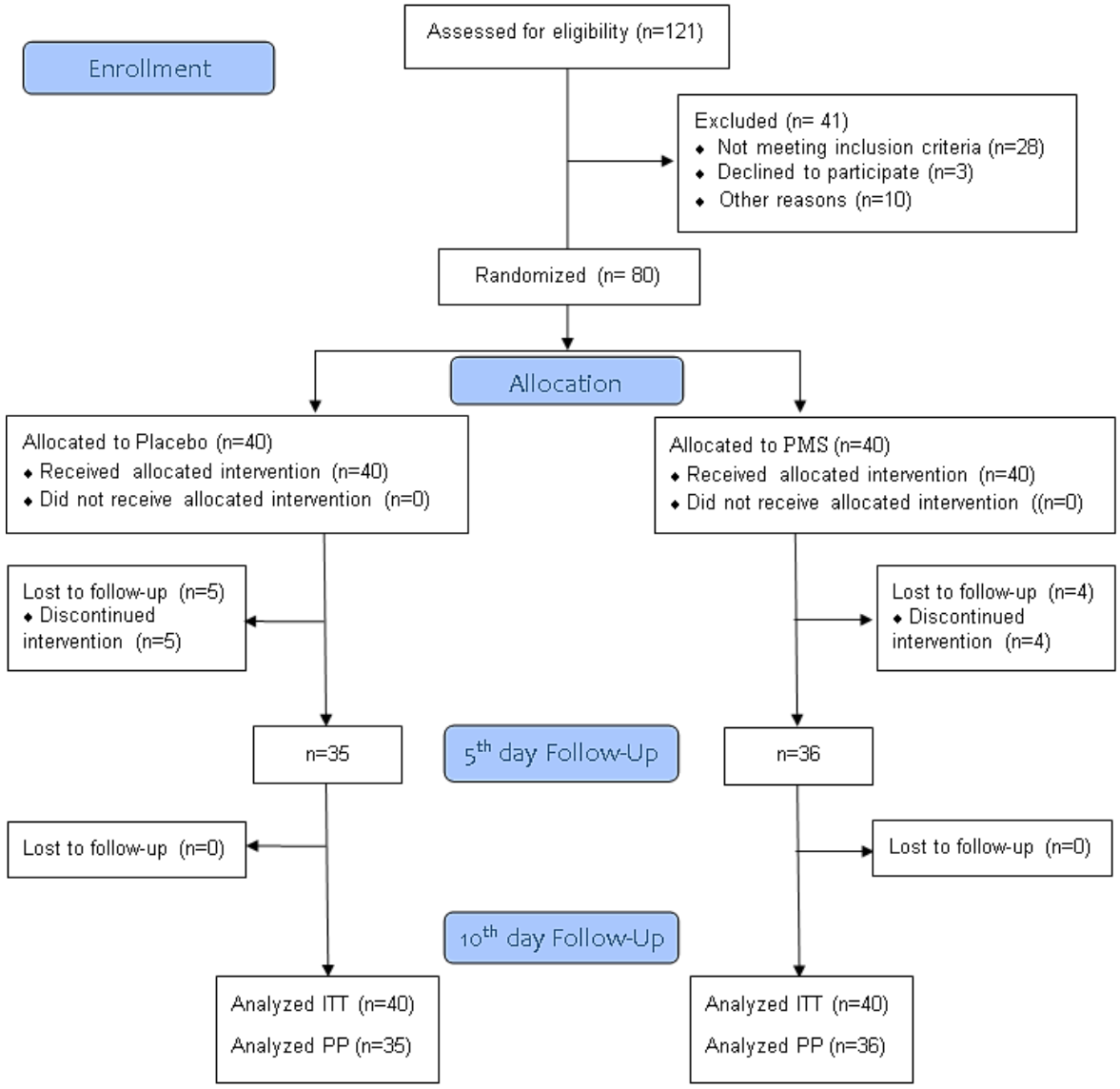

Figure 1. Flow diagram of the study

Table 2. Effect of PMS on the severity of bronchitis

		Base line	Day 5	Day 10	P-value	Partial Eta Square	NNT
Cough	PMS	4.47±0.6	2.80± 1.44	1.63± 0.86	0.001	0.135	3
	Placebo	4.70±0.52	3.45± 1.24	2.30± 1.41			
Dyspnea	PMS	1.52±0.40	1.17± 0.84	0.31± 0.46	0.170	0.024	6
	Placebo	1.52±1.06	1.10± 0.85	1.02± 095			
Sputum	PMS	1.70±1.11	1.20± 0.82	0.37± 0.48	0.005	0.091	3
	Placebo	1.82±1.13	1.53± 0.99	1.34± 1.07			

		Base line	Day 5	Day 10	P-value	Partial Eta Square	NNT
Chest Wall Pain	PMS	1.15±0.97	0.81± 0.79	0.25± 0.44	0.008	0.09	3
	Placebo	1.37±0.77	0.99± 0.93	1.03± 0.95			
Rale	PMS	0.02±0.16	0	0	0.126	0.03	5
	Placebo	0.18±0.56	0	0.06± 0.22			
SCORE	PMS	8.89±2.23	5.99± 1.94	2.57± 1.33	<0.001	0.221	2
	Placebo	9.46±1.64	7.084± 2.14	5.77± 3.09			

PMS: Plantago major syrup

Table 3. Effect of PMS on quality of life

		Baseline	After treatment	P-value	Partial Eta Square	NNT
Physical	Plantago Major	22.54±4.61	29.46±4.40	<0.001	0.232	2
	Placebo	23.27±4.64	25.38±3.87			
Psychological	Plantago Major	20.85±3.78	26.83±3.69	<0.001	0.219	2
	Placebo	21.37±3.80	23.34±4.90			
Social	Plantago Major	11.49±3.32	15.80±2.73	<0.001	0.223	2
	Placebo	11.57±3.63	12.92±3.52			
Total Score	Plantago Major	54.89±10.35	72.10±9.27	<0.001	0.286	2
	Placebo	56.22±10.40	61.64±10.90			

Discussion

In this randomized placebo-controlled trial on the patients with acute bronchitis, PMS was more effective than placebo in the improvement of the bronchitis criteria as well as the QOL. Acute bronchitis, manifested predominantly by cough, is one of the most common infectious diseases referred to the health-care providers. Although acute bronchitis is considered to be a self-limiting condition, the individual complications of coughing due to acute bronchitis are well-known (14).

Treatment methods for acute bronchitis are usually symptomatic and prescribed to relieve upper respiratory symptoms, cough and wheezing. To control acute cough, several classes of drugs are used, including narcotic antitussives, expectorant and antihistamine medications, decongestants, and β2-receptor agonists. However, the review of studies has not reached the conclusion that they are significantly effective (15). Here, complementary and alternative medicine treatments might provide an appropriate choice. *P. major* has traditionally been used to treat inflammations and respiratory infections. This plant contains phenolic compounds and has antioxidant effects (16). Its leaves (containing tannin and mucilage) have been effective in controlling the inflammation of the upper respiratory tract (17). Also, another species of Plantago (*Plantago lanceolata*) had anti-tussive effects in guinea pigs in a study (18). *P. major* has been shown in an old study to be effective in the treatment of chronic bronchitis (11).While our study was on acute bronchitis, in a clinical study, Matev et al. in 1982 investigated the effect of *P. major* preparation on 24 patients with chronic bronchitis. The duration of the intervention was 25-30 days. The results showed that the consumption of *P. major* led to a rapid reduction of subjective complaints and improved objective findings in 80% of cases. Also, the good tolerance of the product and significant effect on some indicators of external respiration were other observations of this study. However, due to not finding the full text of the article and the

uncertainty of the type of questionnaires and the exact methodology of this study, it is not possible to compare it with the present research (11). In a double-blinded, placebo-controlled trial, the efficacy and safety of a herbal product (KalobaTUSS ®), containing P. major, Malva sylvestris, and Inula helenium, was evaluated on 10 children with persistent cough. The participants were treated orally for eight days. Children in the intervention group showed a significant initial decrease in the night and day cough score, and also a shorter duration of cough was observed compared to the placebo (19).

In a clinical study, the effect of a traditional product of licorice in pastille form was investigated in the improvement of chronic cough in seventy participants. The duration of the intervention was 2 weeks and the results showed the effectiveness of licorice pastille in terms of a significant reduction in the cough intensity score compared to the placebo group. In addition, no major side effects were observed during the intervention period as well as during follow-up (20). In the present study, the outcomes measure was the change in BSS from baseline to Day 10. Similar to our study, Lee et al. (2022), used BSS to evaluate the efficacy and safety of a combined Korean formulation (GHX02) on acute bronchitis in patients with BSS ≥5 points. In this randomized placebo-controlled clinical trial, 117 patients in three parallel groups were prescribed herbal product with two doses (960, and 1920 mg/day), or placebo for 7 days. At the end of the study, it was found that the average difference in BSS from the beginning to the day 7 in the intervention groups were higher than that of the placebo group (21).

However, in the aforementioned study, except for cough frequency, other aspects of the BSS were not statistically compared separately. But in our study, this comparison was done separately and it was found that there was a significant effect of *P. major* on the frequency of cough (partial eta square=0.135 and P=0.001), sputum production (partial eta square=0.091 and P=0.005) and chest wall pain (partial eta square=0.09 and P=0.008) compared to placebo group. In another clinical study, the effect of a herbal preparation (DW1601) on 204 patients with acute bronchitis was evaluated using BSS in the baseline and 4 days of medication. Similar to our study, they analyzed the symptom-specific BSS changes as secondary outcomes. At the end of study (day 7), DW1601 was significantly effective in the improvement of the acute bronchitis symptoms as total BSS as well as the cough and sputum component scores of BSS (22).

Since acute bronchitis, manifested by an acute cough, starts following an inflammatory process, the positive effects of the PMS can mainly be attributed to its anti-inflammatory mechanism. Preclinical evidence also confirms the anti-inflammatory effects of this plant. In a study, the anti-inflammatory effects of *P. major* leaf extracts were shown on oral epithelial cells, *in*-vitro by using the NF-kB assay (23). Another experimental study has also confirmed the anti-inflammatory activities of the methanol extract of *P. major* leaves through COX-1 and 12-LOX (24).

It seems that Plantamajoside, the main polyphenol in the extract of *P. major* leaves, might contribute to its anti-inflammatory effect (25). In addition, the immunomodulatory activities of *P. major* may be clinically relevant to many disease processes (26). Also, some chemical compounds (mainly phenolic compounds) present in *P. major* have antiviral activity (27). Health-related QOL is an important outcome parameter for evaluating the effectiveness of therapeutic intervention. In the present study, in evaluating the improvement of QOL, all items including physical, psychological and social domains and also the total scores exhibited significant differences in PMS group in comparison with the placebo ($p<0.001$). After the end of the intervention, it was revealed that there was a significant improvement in the total scores of the LCQ questionnaire and all its subsections in the PMS group compared to the placebo.In addition, PMS was well tolerated for up to 10 days. No specific adverse effect was specified in the follow-ups. One of the strong points of our trial is the constant and close follow-ups of the participants using telephone calls every three days. Patients were learnt about the study progression, filling in the forms, probable problems, and complications. We lost 9 participants during the study. Despite the phone call, they did not attend the clinic for 5^{th} and 10^{th} days of follow up.

According to the baseline data there were no significant differences between groups, so that the effect of PMS could be determined without any confounding factor. Among the weaknesses and limitations of our research, it can be mentioned that the patient survey was conducted during the days when the corona pandemic was prevalent. Due to the limitation in study costs, it was not possible to make an accurate diagnosis with PCR. In addition, it was not possible to separate and evaluate dry and wet coughs. Since, based on Persian medicine, PMS probably has the most effect on dry coughs, it would be better if the effect of PMS on dry coughs is investigated in future studies. In conclusion, a statistically significant improvement of acute bronchitis symptoms as total BSS, and its subdomains including the frequency of cough, sputum, and chest wall pain was observed in the PMS group in comparison with the

placebo. PMS also could significantly improve the QOL. The results of the trial designate the positive effects of PMS in relieving the symptoms of acute bronchitis. More multi-center studies with more objective diagnosis and evaluations can pave the way for future research.

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Authors' contribution: Alireza Naderi made acquisition of subjects and data, Hoda Shirafkan planned the study, analyzed and interpreted the data, Zahra Memariani contributed to the conception, drug preparation, and drafted manuscript, Seyyed Ali Mozaffarpur presented the concept, designed the study, and drafted the manuscript. All the authors reviewed the manuscript critically and approved the final manuscript.

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