

The effect of date seed suspension on reduction of severity and duration of diarrhea in pediatrics with gastroenteritis: A double-blind randomized placebo-controlled trial

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ABSTRACT

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Background and Objective: Acute gastroenteritis in children is a major cause of morbidity in the world. This study investigated the effect of suspension prepared from date seed in reducing the severity and duration of diarrhea in gastroenteritis pediatrics.

Methods: Participants in this clinical trial study comprised 140 gastroenteritis pediatrics referred to Abuzar Children's Hospital in Ahvaz. Eligible patients were randomly assigned to experimental and control groups. The intervention group was given 5% date seed suspension in the amount of 12 mg/kg of body weight orally once every 8 hours for 7 days; the control group was administered a placebo three times a day. Then the two groups were compared for severity and duration of diarrhea as well as stool volume.

Findings: The duration and severity of diarrhea were significantly less in children in the intervention group than in the control group ($p<0.05$). The mean duration of diarrhea in the intervention and control groups was 3.508 ± 1.102 and 4.680 ± 4.001 days, respectively. The mean severity of diarrhea decreased at 24 hours (2.0857 ± 0.607 ; 1.8571 ± 0.747), 48 hours (1.7429 ± 0.695 ; 1.2571 ± 0.695), 72 hours (1.1000 ± 0.695 ; 0.7857 ± 0.814), and 96 hours (0.5429 ± 0.629 ; 0.4143 ± 0.577) after the intervention and was lower in the intervention group than the control group, and the difference between the two groups was significant ($p=0.001$). Moreover, stool consistency was higher in the intervention group than in the control group after the consumption of date seed suspension ($p<0.05$).

Conclusion: Our results confirm the effectiveness of the herbal medicine prepared from date seed waste for control and treatment of gastroenteritis.

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Introduction

Gastroenteritis (GE) is one of the most prevalent causes of morbidity and mortality in children worldwide and accounts for approximately 10% of hospital admissions ^[1,2]. Acute gastroenteritis, although usually considered a benign disease, causes 760,000 deaths annually in infants and children under 5 years of age, which is equal to

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15% of total child mortality [3]. An inflammation of the mucous membranes of the gastrointestinal tract characterized by vomiting, fever, abdominal pain, and/or diarrhea [4]. Gastroenteritis is caused by bacterial, viral, and parasitic agents [5]. Although acute gastroenteritis is a common disease and there are many guidelines for its treatment, there are also many contradictions. In 2016, there were 15 guidelines for the treatment of acute gastroenteritis [2]. The goals of treating acute gastroenteritis include preventing water loss, treating dehydration if it occurs, and reducing the duration and severity of annoying symptoms such as nausea and vomiting [5, 6].

Currently, most guidelines have severely limited treatment of gastroenteritis with antibiotics, because excessive use of antibiotics causes antibiotic resistance, significant side effects, and additional costs. [7] Treatment with probiotics and anti-diarrheal agents is sometimes recommended as adjunctive therapy, because such a treatment course can reduce the duration and severity of symptoms [5, 7]. There have been reports of the usefulness of date seed extract in the prevention and treatment of liver disease in mice [8]. In traditional medicine, date seed is considered a tonic and invigorating agent and is used to heal gastric ulcers [9]. The date seed extract is also a rich source of polyphenols, dietary fiber, and antioxidants such as flavonoids [10]. It also has anti-tumor effects, protective effects against gastric ulcers, and anti-inflammatory properties; it is useful in the treatment of digestive problems and chronic diarrhea [11, 12] and can play an effective role in the treatment of intestinal parasites [13].

Takaeidi et al. [14] showed that date seed has no toxicity, and Mansour et al. [15] confirmed the non-toxicity of date kernel oil. Al-Farisi and Lee [16] reported that date seed powder, which is used as a staple in the confectionery industry for cookies, sweet breads, and pastries, is high in fiber and antioxidants [16]. Date seeds are the main reservoirs of phytosterols and have been used since ancient times to treat hormonal diseases. Saryono et al. [17] showed that malondialdehyde levels decreased significantly in women after they consumed date seeds, while the mean activities of superoxide dismutase, glutathione peroxidase, and vitamin E increased after the consumption of date kernel powder. They concluded that date seed powder increases antioxidant status and reduces oxidative damage in premenopausal women [17].

Date fruit is a strong disinfectant and destroys harmful bacteria in the digestive tract [18, 19]. Reports on the usefulness of date kernel extract in the prevention and treatment of liver diseases in mice have also been published [20]. Clearly, date kernels have many benefits that need to be investigated. Currently, there are no clear indications for antibiotic treatment in cases of gastroenteritis, and it should be noted that overuse of antibiotics leads to antibiotic resistance, significant side effects, and additional costs. As no comprehensive study into the effects of date seed suspension on reducing the severity and duration of diarrhea in gastroenteritis patients in Iran, such a study seems necessary. Therefore, the current study aimed to assess the effects of date seed suspension on reducing the severity and duration of diarrhea in children with gastroenteritis.

Methods

Study design and participant

This double-blind, randomized, controlled clinical trial study was performed in 2020 on patients with gastroenteritis who were referred to Abuzar Children's Hospital in Ahvaz, Iran, a 240-bed specialized and sub-specialized center for children. Participants were assigned to the intervention and control groups randomly (based on a table of random numbers), and sampling was also done randomly. Because the optimum population size is unknown, and information about the variance of the population is not available, the sample size was calculated based on a 95% confidence interval and accuracy of 0.02 using the following formula:

$$N = [(Z\sigma/2\epsilon)^2] / \epsilon \quad N = (1.96 \times 0.6)^2 / 0.02 = 70$$

Thus, the number of samples in each group in this study was determined to be 70 patients. In total, 140 eligible patients (Figure 1) with acute gastroenteritis were randomly divided into the intervention (n=70) and

control (n=70) groups and received one of the following treatments: for the intervention group, 5% in 12 mg per kilogram of body weight date seed suspension was administered orally every 8 hours for 7 days. For the control group, a placebo was given every 8 hours for 7 days. The placebo had no difference in color, odor, size, or appearance from the date seed suspension. Patients with symptoms of diarrhea who were referred to and were hospitalized in Abuzar Children's Hospital, Ahvaz, and all patients who had underlying diseases, such as colitis, fever, etc., were excluded. Those who had no problems other than diarrhea were included in the study. All treatments and placebos were prepared by two professors of Pharmacy at Jundishapur University of Medical Sciences and were placed in similar but numbered bottles. Everyone else was blinded to the contents of the bottles. The amount of drug or placebo to be administered was determined based on the opinion of a pediatric gastroenterologist and two pharmacists and was prescribed and monitored by a pediatrician and members of the nursing staff of Abuzar Hospital. The parents of the patients provided written informed consent for the child to participate in the study. All legal procedures, including the code of ethics and prescribing procedures were approved and licensed by the Jundishapur University of Medical Sciences.

At baseline, no difference was found between the two groups in terms of gender, age, diet, weight, duration of diarrhea, or degree of hydration. Inclusion criteria were patients with gastroenteritis who had an episode of mild to moderate acute diarrhea (more than four times, watery stools based on Bristol criteria), the occurrence of symptoms for less than or equal to 24 hours (1 day), age between 12 and 96 months, and no drug treatment before entering the study. Patients with any of the following conditions were excluded: severe dehydration, abnormal findings such as blood in the stool, frequent vomiting, intolerance to the drug, having another illness or taking other medication during the study, patients with surgical issues such as acute abdominal surgery, immune deficiency, failure to adhere to the treatment protocol or patient withdrawal from the study.

For the intervention, 200 mg of sodium benzoate was dissolved in water, 350 mg of invert sugar, 30 ml of sorbitol 70%, 500 mg of dissolved PEG4000, 500 mg of water-soluble sodium monolaurate, and 2500 mg of water-soluble PVP were added. The mixture was stirred for 30 minutes. Then, 5 g of date seed powder dispersed in water was added to the solution and stirring was continued for another 60 minutes. Next, 300 mg of Xanthan gum dispersed in 5 ml of water, 100 mg of citric acid, 300 mg of sodium citrate, 200 mg of disodium edetate, 200 mg of sucralose, and 130 mg of sodium saccharin were dissolved in water, added to the solution, and stirred for one hour until homogenized. Finally, 6 mg of permissible food coloring and 0.3 g of flavoring were added, the solution was reduced to 100 ml with distilled water, and the pH of the solution was adjusted to 6-5. The contents of the placebo were the same as those of the main product minus the date seed powder.

The duration and intensity of diarrhea, as well as stool volume and consistency, were assessed and recorded on the first, second, third, and seventh days as well as at the end of the study (one week). In this study, an attitude questionnaire was designed to collect information. The questions were explained and justified to the parents, and the questionnaires were completed in person at Abuzar Children's Hospital. Participants scored the consistency of the stool as natural, loose, watery, or very watery with a score of 1 to 4 points, respectively. Stool forms in this study were defined as natural (shaped stools) (Types 1-2), loose (despite not having stools, no clear water can be seen in them) (Types 3-4-5), watery (stools with blue backgrounds with stiff hairs) (Type 6), and very watery (The presence of water only in the stool) (Type 7) ^[21]. For the stool volume variable, scores of 1 to 3 were considered for the options of low, medium, and high volume. Low (less than half a cup), medium (one to half a cup), and large (more than one cup) volumes were defined and interpreted as such after analysis. The frequency of diarrhea is a small scale that was analyzed based on quantitative numbers.

Statistical analysis

Statistical analysis was performed by SPSS software Version 22 (IBM, Chicago, USA). In the current study, descriptive statistics were presented as mean \pm standard deviation (SD) for quantity values. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for the normality of data. To compare the variables, the

independent sample t-test and Chi-square test were conducted for proportion evaluation. A p -value of less than 0.05 was considered significant.

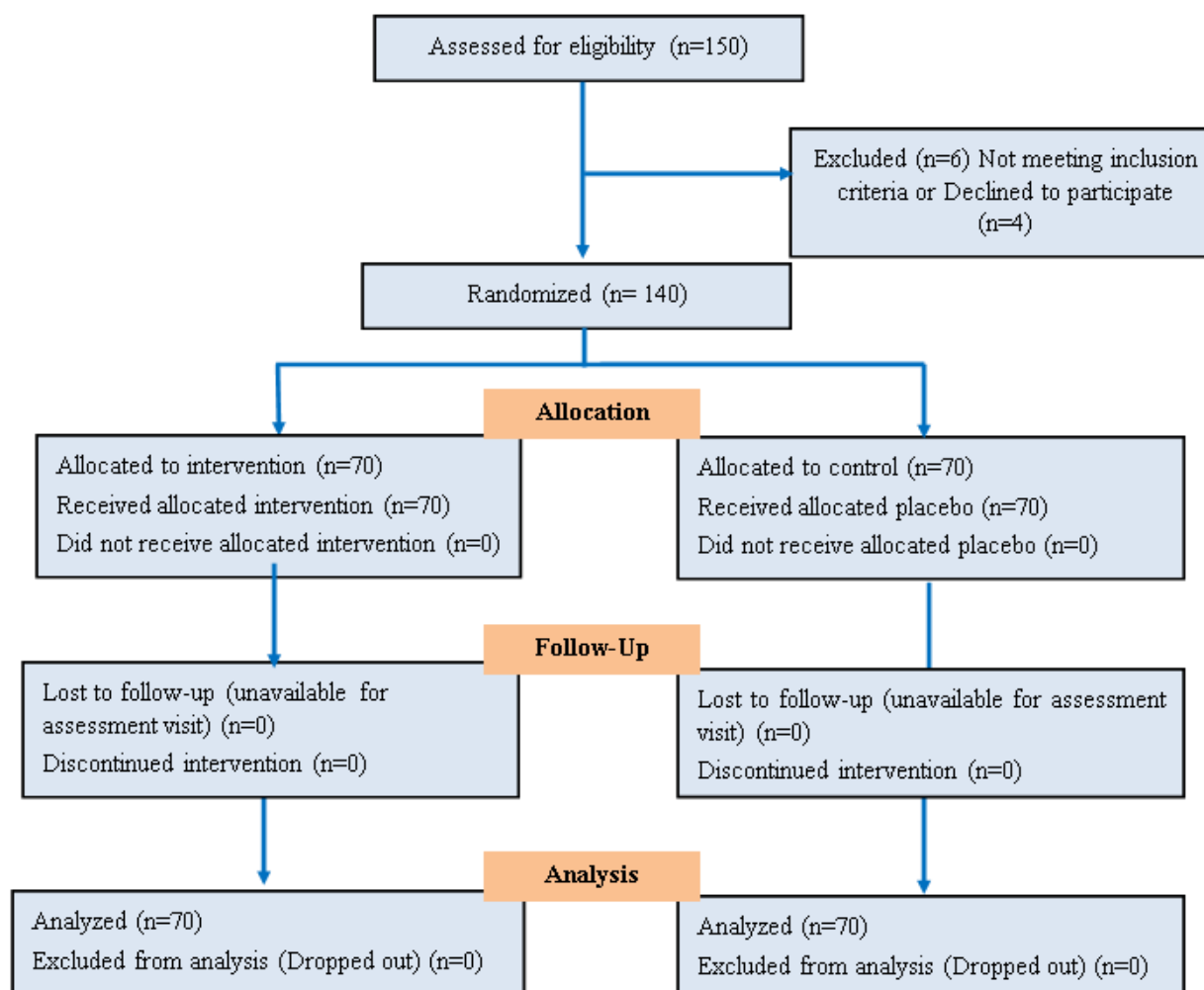


Figure 1. CONSORT flowchart of the study

Results

The overall mean age of participating children was 31.5 ± 19.6 months; children in the intervention and control groups were aged 37.2 ± 25.5 and 23.8 ± 11.8 months, respectively. In the control and intervention groups, females comprised 26.43% and 17.86%, respectively; males accounted for 23.57% and 32.14%, respectively. According to the results, the duration of diarrhea was significantly lower in children in the intervention group than in the control group ($p=0.03$). The mean duration of diarrhea in the intervention and control groups was 3.508 ± 1.102 and 4.680 ± 4.001 , respectively. The mean severity of diarrhea decreased at 24 hours, 48 hours, 72 hours, and 96 hours after intervention and was lower in the intervention group than in the control group with a significant difference between the two groups ($p=0.001$) (Table 1). This difference between the two groups was observed over time, indicating that the time variable and their interaction are also significant.

None of the patients showed any complications during the research and drug (supplement) consumption. Any patient with a positive stool test was excluded from the study. Patients who had an underlying disease or needed drugs other than IV therapy were excluded from the research. Comparisons for 7 days revealed a significant difference in stool consistency between the intervention group and the control group. The intervention group

showed a higher stool consistency than the control group after consuming the date seed suspension ($p=0.01$) (Table 2). Analysis showed that despite the mean stool volume being the same in both groups at admission, after 24 hours, the stool volume in the intervention group was significantly decreased compared to the control group, and considerable differences were observed between the two groups ($p=0.005$) (Table 3).

Table 1. Comparison of severity of diarrhea in control and intervention groups

Time of intervention	Control group (days)	Intervention group (days)	Total	p-value
At the beginning of the study	2.6143±.54621	2.8000±.46935	2.7071±.51588	0.001
24 hours	2.0857±0.60775	1.8571±0.74767	1.9714±0.68848	0.001
48 hours	1.7429±0.69545	1.2571±0.69545	1.5000±0.85242	0.001
72 hours	1.1000±0.69545	0.7857±0.81459	0.9429±0.79360	0.001
96 hours	0.5429±0.62983	0.4143±0.57717	0.4786±0.60535	0.001
Seventh day	0.1286±0.37769	0.2286±0.51560	0.1786±0.45309	0.001

Table 2. Comparison of stool consistency in control and intervention groups

Time of intervention	Control group (days)	Intervention group (days)	Total	p-value
At the beginning of the study	3.3714±1.14425	3.5429±1.15075	3.4571±1.14660	0.01
24 hours	2.5429±1.15075	2.1429±1.31089	2.3429±1.24526	0.01
48 hours	2.1429±1.12012	1.2714±1.22677	1.7071±1.24944	0.01
72 hours	1.4286±0.95662	0.7571±0.96962	1.0929±1.01709	0.01
96 hours	0.5714±0.84393	0.4000±0.66811	0.4857±0.76324	0.01
Seventh day	0.0571±0.23379	0.1000±0.30217	0.0786±0.27003	0.01

Table 3. Comparison of stool volume in control and intervention groups

Time of intervention	Control group (days)	Intervention group (days)	Total	p-value
At the beginning of the study	2.4857±0.86381	2.4429±1.00196	2.4643±0.93232	0.005
24 hours	1.9286±0.72874	1.6286±0.87097	1.7786±0.81415	0.005
48 hours	1.4857±0.75648	1.0000±0.86811	1.2429±0.84710	0.005
72 hours	1.0000±0.65938	0.5143±0.60775	0.7571±0.67719	0.005
96 hours	0.4571±0.58199	0.2857±0.48582	0.3714±0.54102	0.005
Seventh day	0.0571±0.23379	0.1000±0.30217	0.0786±0.27003	0.005

Discussion

The current study evaluated the therapeutic effects of date seed suspension in reducing the severity and duration of diarrhea in children with gastroenteritis. Date seed is one of the wastes obtained during date processing which can be used for different benefits because of its various minerals, fibers, and essential fatty acids. The results of our study showed that the duration and severity of diarrhea were significantly lower in the intervention group than in the control group. It was also observed that after treatment, patients in the intervention group had higher stool consistency and lower stool volume than the control group. The results of the current research are consistent with those of Garba et al., [22] who showed that date kernel has antimicrobial potential against diarrhea. In another study, researchers investigated the effects of date seeds on the gastrointestinal tract of rats. Chemical analysis showed that date seed extract, and especially date seed sap, was richer in sugars and minerals [23]. The researchers reported that date seed extract significantly and dose-dependently improved gastrointestinal function, while palm sap slightly increased it. They also pointed out that date seed played a role in reducing the severity of diarrhea in patients, and its use was considered effective in reducing the severity of constipation [23]. Their findings are consistent with those of the current study. In another study, Megbo et al. [24] assessed the anti-diarrheal effect of date seed extract. Phytochemical screening of date seeds showed the presence of saponins, tannins, glycosides, flavonoids, and alkaloids. The anti-diarrheal activity of date seed

extract was significant. The findings of this study were similar to those of the current research. The current results showed that the date seed suspension was a medicinal substance with anti-diarrheal properties, which may explain the rationale for using date seeds as an anti-diarrheal agent in traditional medicine. Similar to our results, previous studies have reported that the date kernel has protective effects in chronic diarrhea [20, 25]. According to previous studies, date seeds are a unique source of fiber. Soluble fiber promotes the growth of beneficial bacteria in the gut and delays the passage of food from the stomach to the gut [26]. It should be noted that the metabolism of fibers and resistant starches leads to the production of short-chain fatty acids. These substances are considered in physiological amounts as fuel for colonocytes, and they improve the absorption of water and salt and help regulate bowel movements [27]. As diarrhea begins to improve, adding more fiber may help improve normal mucosal function, increase water and electrolyte absorption, and increase stool hardness [28]. The phenolic compounds in date seeds are mainly phenolic acids and flavonoids, which have been reported to have beneficial properties (antioxidant, anti-cancer, and cardiovascular disease prevention) [29]. Previous studies have reported the effect of *Phoenix dactylifera* seeds on diabetic rats through the inhibition of antioxidants and free radicals [30]. Treatment with probiotics has also been previously recommended as an adjunctive treatment because it can help reduce the duration and severity of symptoms. Moreover, previous studies have reported that the polysaccharides isolated from date kernels showed a resistance to digestion that is comparable to or even better than inulin (a natural polysaccharide found in the roots of many plants) and increased the survival time of probiotic bacteria. The ability to absorb oil and retain water for polysaccharides isolated from date kernels is also comparable to that of dietary fibers and much more than that of inulin.

Limitations of the study

The current study encountered a limitation in the sample size, which can play an important role in confirming the results. It is suggested that a study be conducted that has a larger sample size and considers other factors to investigate the effect of date seed suspension on patients with gastroenteritis.

Conclusion

According to the study results, the polysaccharides isolated from date kernel showed comparable and even better probiotic ability than inulin. Furthermore, they can be a good option for treating diarrhea in children because of their ability to retain water and absorb oil and their favorable antioxidant activity [31]. Generally, the results of the current study showed that the duration and severity of diarrhea in children of the intervention group were significantly less than that of the control group. Also, in the intervention group, Moreover, after consuming date kernel suspension, children in the intervention group had a higher stool consistency than the control group.

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Ethical considerations

The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences ([IR.AJUMS.REC.1398.960](#)). Informed consent was obtained from all parents. This trial was registered in the Iranian Registry of Clinical Trials ([IRCT20200202046341N1](#)).

Authors' contribution

N.M, A.Z, M.A, N-SH-M, N-SH and were the principal investigators of the study. N.M, A.Z and M.A were included in preparing the concept and design. N-SH and A.Z revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the

manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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Conflict of interest

The authors have no conflict of interest to declare.

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