

Original Article



Efficacy of Rhubarb (*Rheum ribes* L.) Syrup in Children with Acute Diarrhea: A Randomized, Double-Blind Clinical Trial

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Abstract

Background: Diarrhea is a leading cause of death in infants and children. This study aimed to evaluate the efficacy of rhubarb syrup in improving acute diarrhea in children.

Methods: This double-blind clinical trial was conducted on 1-6-year-old children with acute viral diarrhea referred to Amirkola Children's Hospital, Babol, Iran, from October 2021 to October 2022. Children were randomly divided into two groups- the intervention group (rhubarb syrup) and the placebo group- and were treated and followed up for 2 weeks. The primary outcome was the number of loose stools, and the secondary outcome was the length of hospital stay and recovery from acute diarrhea. Intention-to-treat (ITT), log-rank tests, and generalized estimating equation (GEE) were used to analyze the data. A significant level of $P < 0.05$ was set for the present study.

Results: Totally, 96 children were included in the study (two groups of 48 individuals). After the intervention, no statistically significant difference was found in mean diarrhea frequency between the two study groups ($P = 0.809$; $CI = 0.752-1.895$), but the mean frequency of diarrhea at discharge was significantly lower in both groups than at the beginning of the hospital stay ($P < 0.001$). Statistically, no significant difference was observed between the study groups in the duration of recovery from the start of treatment ($P = 0.296$; $CI = 2.71-3.28$) and the number of hospitalization days ($P = 0.193$). Three cases of gastrointestinal complications occurred in the rhubarb syrup group and one case of skin complications occurred in the placebo group, which was not statistically significant ($P = 0.242$; $P = 1.0$, respectively).

Conclusion: The results of the study show that rhubarb syrup has no significant effect on the treatment of acute viral diarrhea, despite its minor side effects.

Keywords: Medicine, Iranian traditional, Rhubarb syrup, Diarrhea, Child

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Introduction

Diarrhea is the excessive loss of fluids and electrolytes through defecation. Acute diarrhea is the sudden onset of excessively loose stools of more than 10 ml/kg per day in infants and more than 200 g per 24 hours in older children, lasting less than 14 days (1). Diarrhea is a leading cause of death for infants and children around the world, especially in developing countries, and is considered one of the six leading causes of death worldwide (2). Viruses are responsible for up to 40% of severe infectious diarrhea

in developing countries (3).

Oral rehydration is a cheap and easily accessible treatment that significantly reduces mortality. Nevertheless, it cannot reduce the volume and duration of diarrhea (4). Oral rehydration with oral rehydration solution (ORS) solution is 50-100 mL per kilogram of body weight. Moreover, continuing breastfeeding with breast milk and starting feedings after 4 hours every 3-4 hours in children who have oral tolerance are one of the important treatment points (5).



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For the treatment of all children with acute diarrhea, the use of zinc supplements for 14 days (10 mg daily for children younger than 6 months and 20 mg daily for children older than 6 months) is recommended (4). In general, the treatment of diarrhea is based on this principle: basic attention to water and electrolytes and the patient's diet, implementation of nonspecific treatments, and specific treatments (5). In the treatment of diarrhea, plants including rhubarb, which has anti-inflammatory properties and balances the function of the intestine (treatment of constipation and diarrhea), can also be used (6).

Plants are a valuable source of various antimicrobials due to secondary metabolites and other chemicals produced by the plants to defend against microbial attack. Rhubarb is a plant native to Western Asia that is used in traditional medicine for its antidiarrheal effects, among other benefits (7).

Based on previous studies on rhubarb root extract with rhubarb as a digestive system activator, it is known to transport bile salts and stimulate liver secretion. Rhubarb has anti-inflammatory properties and a balancing effect on intestinal activity (treating constipation and diarrhea). Taking rhubarb syrup is suitable for treating diarrhea, anemia, and anorexia, as it contains amounts of iron and is a good tonic. It is even suitable for strengthening and weakening patients (6,8).

Therefore, considering the problems in the treatment of acute viral diarrhea in children and the lack of definitive drug treatment to reduce the complications and the number and extent of acute viral diarrhea, it seems necessary to find an effective treatment.

Hence, because of the limited studies on the effect of rhubarb in acute viral diarrhea, especially in children, and the lack of complications with the use of rhubarb syrup in previous studies (7), this study aimed to evaluate the efficacy of rhubarb syrup in improving acute diarrhea in 1-6-year-old children.

Methods

Type of study and samples: This double-blind clinical trial was conducted on 1-6-year-old children with acute viral diarrhea referred to Amirkola Children's Hospital, from October 2021 to October 2022.

Inclusion criteria were 1-6-year-old children with acute viral diarrhea (loose stool more than three times daily) in the past 72 hours, acute gastroenteritis, fecal white blood cell count less than 5/ high power field (HPF) and no blood in the stool, and mild to moderate dehydration according to the Mana criteria (9).

Exclusion criteria include more than three days since onset of diarrhea, children treated with antidiarrheal drugs or antibiotics in the last three days, toxic colitis during diarrhea, pneumonia, meningitis, sepsis, cysts of *Entamoeba histolytica*, trophozoites of *Giardia lamblia*

in stool, bloody stool (infectious and noninfectious bloody diarrhea), consumption of powdered milk, severe malnutrition (weight to age less than 60% or weight to height less than 70%), known history of chronic disease or any type of food allergy, taking probiotics, and in cases where diarrhea caused complications such as seizures or ileus, immunodeficiency, other infections including urinary tract infections. Diarrhea was defined as the passing of loose or liquid stools at least three times or more frequently than normal (10,11). Acute diarrhea was also defined by duration of less than two weeks (12).

Interventions

The children with diarrhea were examined by a gastroenterologist (corresponding author) and a pediatric resident (first author). A physical examination was performed to delineate the type, duration, and severity of diarrhea and to evaluate the related clinical features such as fever, dehydration, vomiting, pain, and abdominal distension. Demographic data such as age, gender, and weight were collected at the children's first visit.

Children who experienced vomiting and diarrhea together were included in the study after the vomiting improved and they were able to resume eating. In dehydrated children, fluid therapy was administered according to the World Health Organization (WHO) guidelines, with oral or intravenous fluid therapy as appropriate. Children who had severe dehydration and required intravenous fluid infusion were also included in the study after dehydration was corrected and stabilized. All children with acute diarrhea were prescribed 20 mg of zinc sulfate syrup daily according to the WHO guidelines (5).

Randomization

Using a table with random numbers, children were divided into two groups: Group A (rhubarb syrup + standard treatment (rehydration and zinc sulfate) and group B (control group), which received the standard treatment. Randomization was performed by permutation blocks of size 4. In this method, the same number of rhubarb syrup (A) and placebo (B) were randomized in each block. This work was performed by a statistician. The doctor, nurse, and patient were blind to the type of drug.

Blinding

To blind the doctor, nurse, and patient, the rhubarb syrup and placebo were prepared in completely identical designs and bottles in terms of shape, color, and odor. To conceal the treatment process, each bottle of rhubarb syrup/placebo was assigned a three-digit code. Upon entry into the study, the drug code was recorded in the file and questionnaire after rhubarb syrup/placebo was administered to the patient. In case of possible complications, the code was

opened. Otherwise, the codes were opened at the end of the study and during the analysis.

Extraction

Fresh above-ground branches of the rhubarb plant were obtained in May in the mountainous regions of the Chalus Road. The above-ground branches were cut into small pieces. Then, 500 mL of distilled water was added per 100 g of crushed stems and boiled for 15 minutes. The boiled contents were filtered in the laboratory with filter paper and concentrated in a bain-marie device.

Rhubarb syrup design

Rhubarb syrup was based on USP 34 simple syrup. USP simple syrup based on water and sugar was 66.7%. The prepared syrup was filled in 120 mL amber bottles with a label.

The preparation of *Rheum ribes* and placebo syrup was carried out in the laboratory of herbal medicine of Shahid Beheshti Faculty of Pharmacy in Tehran. The placebos were prepared according to a simple formula based on the standard USP pharmaceutical syrup, including the standard color, taste, and appearance similar to rhubarb syrup. Finally, both products were put into the same bottle and packaging.

It is noteworthy that the rhubarb syrup was prepared on the standard basis of total flavonoid content by spectrophotometry and using Rutin solution and aluminum chloride as reagents and standard control. In the syrup, the total flavonoid content was 0.356 MG/ML. In addition, the total flavonoid content was 13.7% Rutin.

The target dose in group A was 2.5 mL for children weighing less than 15 kg or 5 mL for children weighing more than 15 kg every 6 hours for 5 days (7). In group B, only a placebo was administered at the same dose.

Outcomes

The primary outcome was the number of loose stools, and the secondary outcome was the length of hospital stay and recovery from acute diarrhea (Bristol score less than 5). The children studied were treated and followed up for 2 weeks. After the children's hospitalization, the frequency of defecation, duration of hospitalization, and duration of full recovery from diarrhea were recorded using the Bristol stool chart.

Duration of recovery from acute diarrhea is defined as the time interval between admission and cessation of diarrhea or first normal bowel movement, which corresponds to a score below 5 on the Bristol stool table (13).

Primary and secondary outcomes were recorded during hospitalization, and mothers were asked to record the data on the protocol form after discharge and to report them by telephone during follow-up.

From the beginning of treatment until two weeks later, a list was made to record the adverse effects of the drug.

Parents were also advised to accompany their children or to contact the pediatric resident (first author) in case of side effects.

Side effects of the drug were assessed by history, physical examination, and lab data. These included gastrointestinal side effects (e.g., exacerbation of diarrhea and vomiting) and skin side effects (e.g., rash), and other side effects, such as liver and kidney side effects, were monitored by lab tests.

Data analysis method

The collected data were entered into Excel for statistical analysis. For the statistical analysis of this study, central indices and dispersion indices were used in the descriptive statistics section.

In the inferential statistics section, the generalized estimating equation (GEE) was used to test the hypotheses of the study using parametric tests (student *t* test, chi-square) and to check the effect of rhubarb syrup on acute diarrhea, and survival analysis and log-rank test were used to examine the length of hospital stay and recovery time in two groups. Intention-to-treat (ITT) method was also used for data analysis. The data were analyzed using SPSS 25 at a significance level of $P < 0.05$.

Results

In this study, 106 children were examined, of whom 96 were eventually enrolled in the study, and 89 children continued treatment until the end of the study. The process of how the children were enrolled in the study is shown in the following CONSORT flow diagram (Figure 1).

The children were categorized into two groups of 48 children each. The background characteristics of the children are shown in Table 1.

According to Table 1, no statistically significant difference was found between the study groups in terms of weight, age, height, and gender of the children, and the two groups were similar.

Vomiting (87, 90.6%) was the most common accompanying symptom of diarrhea in the study children, which was not different between the study groups (87.5% in the intervention group and 93.8% in the placebo group; $P=0.294$). The mean diarrhea frequency per day was 7.39 ± 3.73 (minimum and maximum 3 and 20 times, respectively), with no statistically significant difference between the study groups and similar between the two groups (7.41 ± 3.89 for the rhubarb syrup group and 7.37 ± 3.61 for the placebo group; $P=0.957$).

Children's dehydration was assessed using the Mana criteria (9), and most children (63, 65.6%) had moderate dehydration. Statistically, no significant difference was observed between the two groups in terms of patient dehydration ($P=0.955$).

Mean diarrhea frequency at discharge decreased significantly compared to the start of hospitalization in

Table 1. Background characteristics of the children

Variable	Total (96 children)	Rhubarb syrup (48 children)	Placebo (48 children)	P
Age (month), Mean (SD)	28.41 (17.43)	29.68 (19.16)	27.14 (15.62)	0.478*
Weight (kg), Mean (SD)	12.43 (3.07)	12.56 (3.09)	12.29 (3.07)	0.667*
Height (cm), Mean (SD)	90.08 (15.77)	90.22 (17.02)	89.94 (14.58)	0.931*
Gender, No. (%)				
Male	53(55.2%)	25 (52.1%)	28 (58.3%)	0.538**
Female	43(44.8%)	23 (47.9%)	20 (41.7%)	

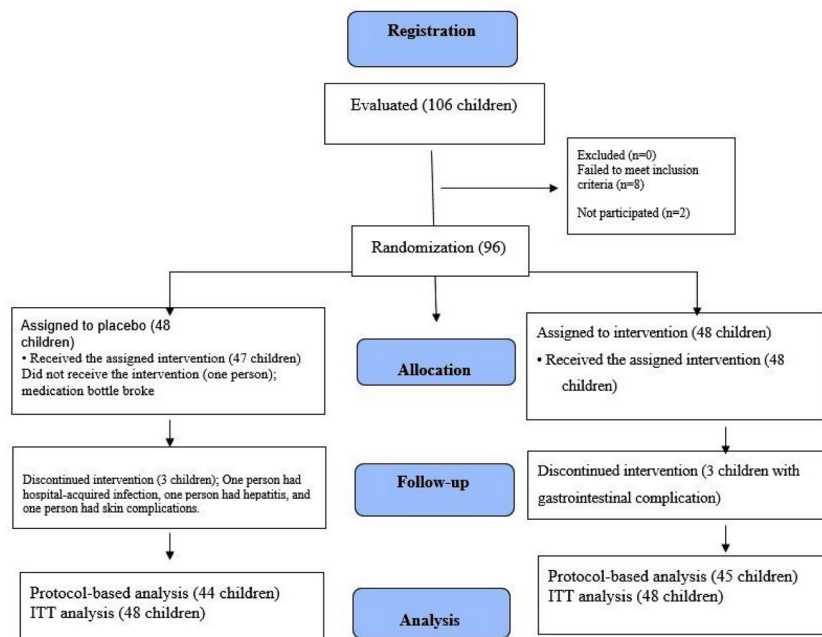
*T test; ** Chi-square test

Table 2. Comparison of mean stool excretion at the time of hospitalization and discharge between the study groups

Time	Group			P*	P**
	Total (85 children) No. (%)	Rhubarb syrup (42 children) No. (%)	Placebo (42 children) No. (%)		
At the time of hospitalization	7.02 (3.52)	6.90 (3.46)	7.13 (3.61)	<0.01	0.809
At the time of discharge	1.27 (0.98)	1.29 (0.94)	1.26 (1.02)		

* Comparison of mean stool excretion at the time of hospitalization and discharge.

** Comparison of the mean stool excretion at the time of hospitalization and discharge between the study groups.

**Figure 1.** CONSORT flow diagram

both study groups ($P < 0.01$), but no statistically significant difference was seen between the two study groups ($P = 0.809$ and $CI = 0.752-1.895$) (Table 2).

According to the Kaplan-Meier test, no statistically significant difference was observed in recovery time from the start of treatment between the study groups (median 3 days for the rhubarb syrup group and 4 days for the placebo group; $P = 0.296$ and $CI = 2.71-3.28$) (Figure 2).

The Mann-Whitney U test was applied to compare the number of hospitalization days between the study groups. There was no statistically significant difference in the number of hospitalization days between the study groups

(median: 4 days (interquartile range (IQR): 2 days) for the rhubarb syrup group, median: 4 days (IQR: 3 days) for the placebo group; $P = 0.193$) (Figure 3).

In general, four cases of treatment complications were observed, 3 (6.3%) cases in the rhubarb group and 1 (2.1%) case in the placebo group.

There was no statistically significant difference between the study groups in terms of complications ($P = 0.617$). Three cases of gastrointestinal complications occurred in the rhubarb syrup group, and one case of skin complications occurred in the placebo group; none of these complications was statistically significant ($P = 0.242$

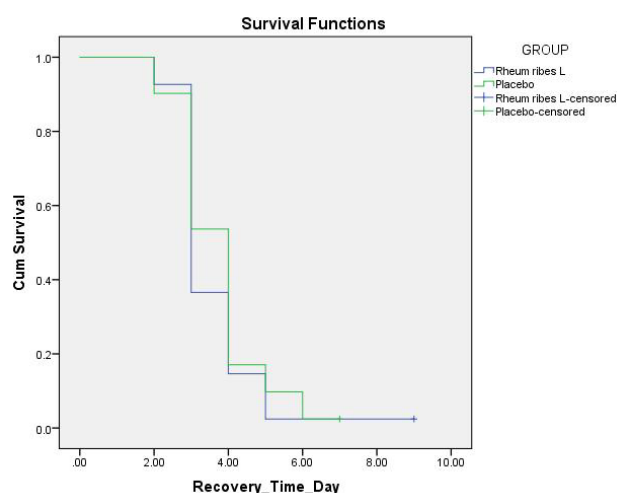


Figure 2. Time to recovery in the study groups (survival analysis)

and $P=1.0$, respectively). All children who experienced complications had the drug discontinued, and did not discontinue treatment.

In the ITT analysis of the two study groups, the mean diarrhea frequency was significantly decreased at the time of discharge compared with the beginning of hospitalization ($P<0.01$), but there was no statistically significant difference between the two study groups ($P=0.420$).

Discussion

This study was conducted to evaluate the effectiveness of rhubarb syrup in improving acute diarrhea in 1-6-year-old children. In the two study groups, the mean diarrhea frequency decreased significantly at the time of discharge compared with the beginning of hospitalization, but there was no statistically significant difference between the study groups. There was no statistically significant difference between the study groups in the number of days of hospitalization and the duration of recovery from the start of treatment.

The results of the present study are comparable to the only similar study conducted on children with acute diarrhea. Khiveh et al (7) studied the effects of rhubarb syrup (*Rheum ribes* L.) on dysentery in children. In their study, 150 children with suspected dysentery caused by *Shigella* were examined.

The average duration of fever and diarrhea was significantly shorter in the rhubarb syrup group than in the placebo group. In addition, patients in the rhubarb syrup group showed shorter duration of fever and abdominal pain.

Based on the results of their study, it was concluded that *R. ribes* syrup can be proposed as a complementary treatment for children with diarrhea. Although the results of their study showed significant superiority of rhubarb

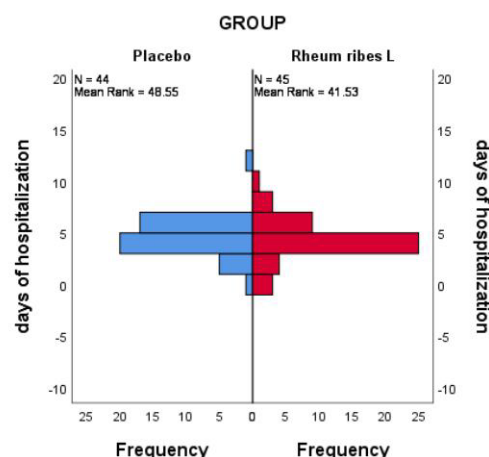


Figure 3. Comparison of the number of hospitalization days between the study groups

treatment over placebo, the present study suggested that rhubarb treatment was no more effective than placebo in treating patients with acute diarrhea.

The difference in the pathogen among the patients in the two studies may be the reason for this difference in results, as their study involved bacterial diarrhea and the present study involved viral diarrhea.

Several laboratory studies have also shown that rhubarb has an antibacterial effect, and these results may be the reason for the better effect of rhubarb syrup on bacterial diarrhea.

In a study, Salehi et al investigated the antimicrobial effects of aqueous and alcoholic extracts of rhubarb (*R. ribes*) on some foodborne pathogenic bacteria under laboratory conditions. According to the results, aqueous and ethanolic extracts of rhubarb stem and leaf had a good inhibitory effect on *Staphylococcus aureus* and *Escherichia coli* bacteria (14). The study of Kosikowska et al (15), Kazemi Darsanaki and Parsa Lisar (16), and Fazly Bazzaz et al (17) also confirmed this result.

Qin et al studied the dual diarrheal and antidiarrheal effects of rhubarb and its possible mechanism. Their results suggest that rhubarb has both diarrheal and antidiarrheal effects due to the coexistence of anthraquinones and tannins. The bilateral effects could be one of the reasons or the reason for the adverse effects of the long-term use of rhubarb as a cleanser (18).

Studies have confirmed the antibacterial effect of rhubarb, but studies on the antiviral effect of rhubarb are very limited. It is recommended that more studies be conducted on the antiviral effects of rhubarb.

One of the limitations of the present study is that the type of viral pathogen causing diarrhea could not be determined. Since the present study is the only clinical trial that investigated the efficacy of rhubarb syrup in the treatment of acute viral diarrhea, the ability to compare

the results with other studies is very limited.

Most of the studies are biochemical and basic science studies. Clinical studies on various topics have generally been conducted on the adult population, some of which have to do with the effect of rhubarb on the digestive system of patients. The strength of this study is that it was the first study to investigate the efficacy of rhubarb syrup in the treatment of acute viral diarrhea in children. Moreover, the ongoing study was a randomized and double-blind clinical trial, which is another strength.

Conclusion

Despite the decrease in the number of bowel movements in children treated with rhubarb syrup during hospitalization, the efficacy of this treatment was not significantly different from placebo treatment in terms of the number of days of hospitalization and the average decrease in the number of bowel movements. Therefore, the present study concluded that rhubarb syrup did not have a significant effect on the treatment of acute viral diarrhea despite its minor side effects. We recommend further studies in this field.

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Visualization: Sanaz Mehrabani, Shahla Rahbar, Mohammadreza Esmaeili.

Writing—original draft: Sanaz Mehrabani, Shahla Rahbar.

Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study was approved by the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1400.185) and registered in the Iranian Clinical Trials Registry (identifier: IRCT20200105046009N5). To maintain ethical considerations, written informed consent was signed by parents, and all information

from the children was kept confidential.

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