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• Research Article

Effects of rhubarb (*Rheum ribes* L.) syrup on dysenteric diarrhea in children: a randomized, double–blind, placebo–controlled trial

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ABSTRACT

BACKGROUND: *Rheum ribes* L. is a plant native to China, Iran, Turkey, India, and a few other countries. Antidiarrheal activity is considered to be one of its important properties according to various systems of traditional medicine. An increasing rate of bacterial resistance to antibiotics has led to treatment failure in some cases of shigellosis in children, and underlines a need for safe, efficient and valid options.

OBJECTIVE: The purpose of this study is to evaluate the efficacy of *R. ribes* syrup as a complementary medicine for treatment of shigellosis in children.

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: This randomized, double-blind, placebo-controlled trial started with a group of 150 children aged between 12–72 months with suspected *Shigella* dysentery. *R. ribes* syrup or placebo syrup was administered to the intervention and control groups, respectively for 5 days. In addition, the standard antibiotic treatment (ceftriaxone for the first 3 days and cefixime syrup for 2 further days) was administered to both groups.

MAIN OUTCOME MEASURES: Body temperature, abdominal pain, need for antipyretics, defecation frequency, stool volume and consistency and microscopic stool examination were recorded as outcome measures. Any observed adverse effects were also recorded.

RESULTS: Mean duration of fever and diarrhea in the *R. ribes* group was significantly lower than that in the placebo group (P = 0.016 and 0.001, respectively). In addition, patients in the *R. ribes* group showed shorter duration of need for antipyretics and shorter duration of abdominal pain (P = 0.012 and 0.001, respectively). However, there were no significant differences between the two groups regarding the microscopic stool analyses. Furthermore, no adverse effect was reported.

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CONCLUSION: *R. ribes* syrup can be recommended as a complementary treatment for children with *Shigella* dysentery.

TRIAL REGISTRATION: Iranian Registry of Clinical Trial: IRCT2014070518356N1.

Keywords: traditional Persian medicine; herbal medicine; *Rheum ribes* L; rhubarb; dysentery; shigellosis; diarrhea

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1 Introduction

The mortality rate of shigellosis dysentery is still high, especially in children of developing countries.[1] The main treatment is rehydration and administration of antibiotics, but the increasing rate of bacterial resistance to antibiotics has led to treatment failure in some cases. Thus, other safe, efficient and valid treatment options are required for management of shigellosis in children.[2]

The plant kingdom is a valuable source for different antimicrobial agents. This is because of secondary metabolites and other chemicals which are produced by plant for defense against microbial attack.[3]

Rheum ribes L. (Polygonaceae) is a plant native to Western Asia and is grown in Turkey, Iran, India, China and a few other countries.[4,5] In addition to medicinal applications, it is usually considered as an edible fruit and used for making jam or syrup by locals.[6,7] *R. ribes* is a popular herb in different traditional medicine systems and its documentation dates back to *Sen Nung Pents'ao Jing* (22–250 A.D.).[8] In these systems, *R. ribes* is employed for treating a variety of symptoms and diseases, such as emesis, diabetes, hypertension, obesity, and various psychological disorders.[9,10] Moreover, one of its important uses in different nations' traditional medicines is antidiarrheal activity. It is also used for gastrointestinal hemorrhages.[11,12]

In Iran, *R. ribes* is called *Rivas*.[4] According to traditional Persian medicine, this plant is useful for both fever and dysentery.[13–15] Avicenna (980–1037 A.D.),[16] in his famous book, Canon of medicine, explained about *R. ribes*: Temperament of *Rivas* is cold and dry; it is refrigerant and acts as an antipyretic agent … *Rivas* is beneficial in bilious and bloody diarrhea (*Eshal e Damavy*).[13] Its fruit was also mentioned as an astringent medicine and recommended for treatment of diarrhea by famous Persian physicians, such as *Aghili Shirazi* (1670–1747 A.D.) in *The Storehouse of Medicaments*.[14,17–19]

It is noticeable that different parts of *R. ribes*, such as root and stem, have shown a significant antioxidant activity in previous research.[20,21] *R. ribes* is a rich source of different vitamins such as A, B, C and E. It also possesses several minerals and trace elements including calcium, phosphorus, iron, potassium, sodium, magnesium, zinc, copper and selenium.[22] Previous investigations had shown that the aerial parts of this medicinal plant comprise a variety of active ingredients, such as chrysophanol, physcion, emodin, quercetin, 5-desoxyquercetin, quercetin 3-O-rhamnoside and quercetin 3-O-rutinoside.[23] According to previous studies, *R. ribes* root extract has a significant activity against several Gram-positive and -negative bacteria.[3,24] Also, its stalk and leaves' significant activity against *Shigella spp*. has been documented.[5]

To the best of our knowledge, there have been no clinical studies on the efficacy and safety of *R. ribes* in children with shigellosis. Therefore, this study was designed to evaluate the effects of *R. ribes* on duration of fever, diarrhea and abdominal pain in children with shigellosis dysentery. Additionally, we aimed to assess its efficacy on microscopic examination of their stool, stool's consistency and volume, frequency of defecation as well as need for antipyretics. A safety assessment was also done simultaneously with the evaluation of its efficacy.

2 Materials and methods

2.1 Trial design

This study was a randomized, double-blind, placebo-controlled and parallel-group clinical trial.

2.2 Study setting

This study was conducted in the inpatient ward of Ardakan Ziaei Hospital, Yazd, Yazd Province, Iran, from August 2014 to January 2016. The study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (Code: 17/1/65410). It was registered in the Iranian Registry of Clinical Trials with the registration number of IRCT2014070518356N1. A signed informed consent form was obtained from the parents of each child before enrollment.

2.3 Inclusion and exclusion criteria

Only children aged 12 to 72 months fulfilling the following criteria were enrolled in the study: (1) suffering from diarrhea (loose stool more than 3 times per day) for

previous 72 h, (2) presence of white blood cells (WBCs ≥ 5 per microscopic high-power field) in the stool with or without mucus, and frank blood. Children who had been treated with antibiotics or antidiarrheal drugs during the last 3 days were excluded from the study. Other exclusion criteria were the presence of *Entamoeba histolytica* cysts or trophozoite of *Giardia lamblia* in the stool; or suffering from pneumonia, sepsis, meningitis or toxic colitis along with diarrhea. Additionally, stool culture for *Shigella spp*. was requested after enrollment. Children with negative stool culture were excluded at follow-up.

2.4 Randomization, blinding and concealment

The patients were randomized in two arms of the study using sequentially numbered, opaque, sealed envelopes. *R. ribes* and placebo syrups had similar physical properties (e.g., color and taste), and were packaged in identical bottles. Therefore, all participants in both groups were blinded to the study allocation. In addition, the physicians, nurses and data analyst were not aware of the patients treatment groups.

2.5 Clinical management

All the patients were treated by infusion of ceftriaxone (Alborz Daru) (100 mg/(kg·d), in two divided doses) for the first 3 days. Then, treatment was continued for 2 further days using cefixime syrup (10 mg/kg).

2.6 Herbal drug and placebo preparation

Dried *R. ribes* fruits were purchased from a local medicinal herb market (Tehran city, Iran). Taxonomic identification was approved by M. Kamalinejad and a voucher specimen (No. 8092) was deposited in the Herbarium of the Shahid Beheshti School of Pharmacy, Tehran, Iran.

The herbal medicine used in this trial was the syrup made from aqueous extract of the *R. ribes* fruits. Preparation of the *R. ribes* and placebo syrups was done in the Herbal Medicine Laboratory of the Shahid Beheshti School of Pharmacy (Tehran, Iran). Based on the traditional procedure, 1 L of boiling water was added to 100 g of dried fruit and kept in a closed container for 4 h. The water was then removed under vacuum at 90 °C using a rotatory vacuum evaporator. Sugar solution (50%) was added to the extract to make a final concentration of 50 mg of the extract in each 1 mL of the syrup. Herb-to-extract ratio was then 6:1. The placebo was prepared using the pharmacopoeia simple syrup formula including standard coloring and flavoring agents, and looked the same as the *R. ribes* syrup. Finally, both products were filled in the same opaque bottles and their packages were identical in appearance.

It is notable that *R. ribes* syrup was standardized based on total flavonoid content *via* spectrophotometry using aluminum chloride and rutin solution as reagent and standard control, respectively. The total flavonoid content was 0.356 mg/mL of the syrup. Also the total flavonoid/rutin was 7.13.

Moreover, the syrup was standardized according to the total phenolic content of 2.305 mg/mL. It was determined by the Folin-ciocalteu method, using gallic acid as the reagent.[25]

2.7 Experimental intervention

The dose taken of either syrup was 2.5 mL for children less than 15 kg, or 5 mL for children ≥ 15 kg, every 6 h for 5 days. The prescribed drugs were administered under the supervision of a nurse.

2.8 Outcome measurement

At first, a physician took a medical history followed by a physical examination. Body temperature, abdominal pain, need for antipyretics, defecation frequency and stool volume and consistency were recorded every 8 h for 3 days by a nurse who was blind to the study allocation. In the 4th and 5th day, these data were collected from the children's parents. The process of data collection was done in a timely manner to avoid any recall bias. Additionally, it was supervised and coordinated by Ali Khiveh. Moreover, the following laboratory exams were conducted: (1) Microscopic stool examination was done for the ova, parasites, leukocytes and erythrocytes on days 0, 3 and 5; (2) The stool was cultured for *Shigella spp*. on days 0 and 3; (3) Complete blood count was done on days 0 and 3.

2.9 Statistical analysis

The sample size was calculated considering 5% significance level with 80% statistical power, and minimum clinical significant difference of 27% between the study groups by using

$$N = \frac{(Z_{\frac{\alpha}{2}} - Z_{\beta}) \times 2 \times \bar{P}(1-\bar{P})}{(P_1 - P_2)^2}$$

Additionally, a probable 30 percent drop-out (mainly due to the negative stool culture for *Shigella spp*.) was considered. Finally, 150 participants were randomly allocated into the two study groups. The data were analyzed by the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA), using Student's *t*-test, and chi-square test. *P* values less than 0.05 were considered as significant.

3 Results

3.1 Study flow

In this study, 150 patients were enrolled and randomized in the two groups of the study. A total number of 96 children (47 children in the *R. ribes* group, and 49 children in the placebo group) completed the study and were included in the analysis. Detailed information on eligibility assessment, randomization, follow-up and

analysis of the children in each group is presented in Figure 1.

3.2 Baseline characteristics of the patients

Important demographic and clinical characteristics of the patients in each group are displayed in Table 1. There were no significant differences between the age, gender makeup or fever temperature of the two groups. In addition, all children who completed the study had fever and a positive stool culture for *Shigella spp*.

3.3 Efficacy evaluation

Table 2 presents the mean values of clinical outcome measures in *R. ribes* and placebo groups. The mean duration of fever in the *R. ribes* syrup group was significantly lower than that in the placebo group ((28.80 ± 6.75) h *vs* (50.40 ± 24.74) h; $P = 0.016$). Also, patients in the *R. ribes* group demonstrated a shorter duration of need for antipyretics ($P = 0.012$). Duration of abdominal pain in the *R. ribes* group was also shorter ($P = 0.001$).

Moreover, the duration of diarrhea was significantly lower in the *R. ribes* group as compared with the placebo group ($P = 0.001$). Detailed indicators of diarrhea were all significantly improved in the *R. ribes* group compared to the placebo group. In fact, reduction of stool volume, and defecation frequency to the normal state (i.e., 3 times per day) and mean time for increased stool consistency in the *R. ribes* group were each significantly lower than in the placebo group ($P = 0.009$, 0.016, and 0.001, respectively).

Results of patients' stool examinations are presented in Table 3. There were no significant differences between the mean time of reduction of RBC, WBC and mucus clearance in the *R. ribes* and placebo groups ($P = 0.667$, 1.00, and 0.162, respectively).

3.4 Safety and tolerability

Children tolerated the *R. ribes* syrup well. There were no reports on any minor or major adverse effects during the study follow-ups.

4 Discussion

Medicinal plants have an undeniable position in almost all cultural traditions. They are mainly used for primary health care (such as infectious diseases) and as complementary treatments in developing and developed

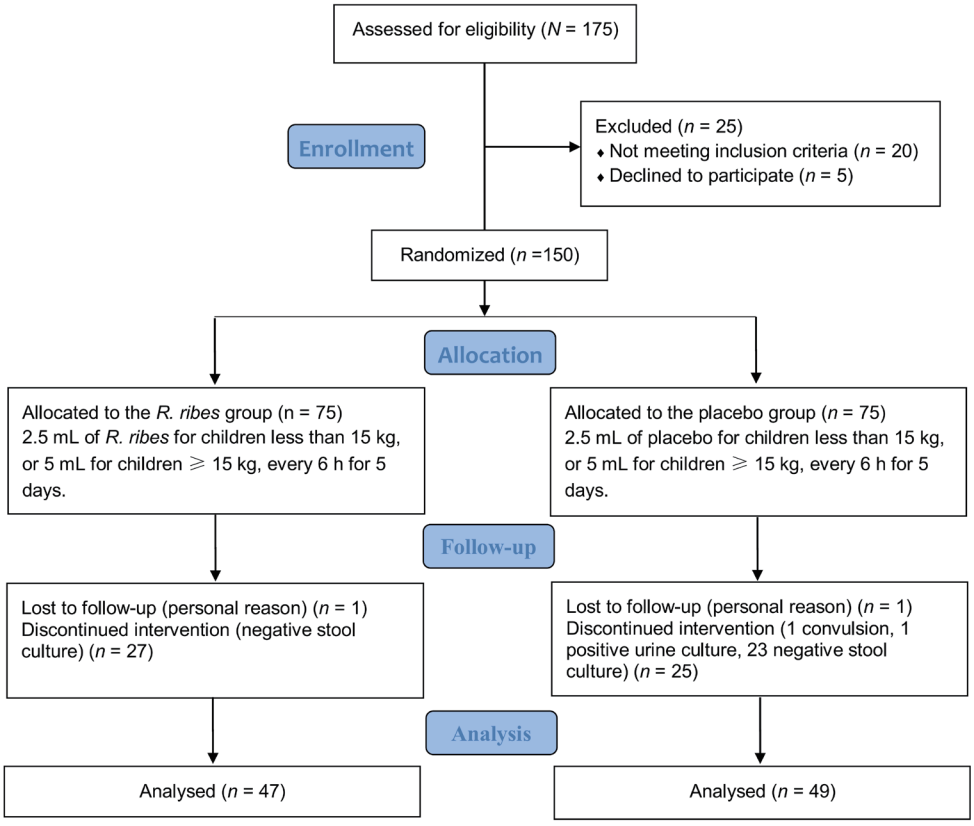

Figure 1 The flowchart of the trial

Table 1 Baseline characteristics of the participants in the two groups of *Rheum ribes* L. and placebo syrups

Item	Rheum ribes L. group (n = 47)	Placebo group (n = 49)	P value
Age (mean ± SD, month)	27.4 ± 12.44	28.50 ± 15.79	0.86
Gender (n, %)			0.36
Male	33 (70.21)	33 (67.34)	
Female	14 (29.78)	16 (32.65)	
Fever (mean ± SD, °C)	38.62 ± 0.48	38.82 ± 0.70	0.47

SD: standard deviation.

Table 2 Comparison of mean duration of improvement in clinical signs and symptoms of shigellosis in the *Rheum ribes* L. and placebo groups

Duration (mean ± SEM, h)	*Rheum ribes* L. group (n = 47)	Placebo group (n = 49)	P value
Cessation of fever	28.80 ± 6.75	50.40 ± 24.74	0.016
Discontinuation of antipyretic	25.60 ± 6.31	48.00 ± 24.72	0.012
Reduction of abdominal pain	25.00 ± 7.93	77.33 ± 4.62	0.001
Duration of diarrhea	22.40 ± 7.35	59.20 ± 21.73	0.001
Reduction of stool volume	21.60 ± 6.58	47.20 ± 26.78	0.009
Decrease of defecation frequency ≤ 3 times/day	16.80 ± 5.90	27.20 ± 10.79	0.016
Increase in stool consistency	23.20 ± 8.80	56.88 ± 23.81	0.001

SEM: standard error of mean.

Table 3 Comparison of parameters of stool examination in the *Rheum ribes* L and placebo groups

Parameter (mean ± SEM, h)	*Rheum ribes* L group (n = 47)	Placebo group (n = 49)	P value
Reduction of RBC in stool	88.00 ± 27.71	72.00 ± 0.00	0.667
Reduction of WBC in stool	81.60 ± 20.24	81.60 ± 20.24	1.000
Clearance of fecal mucus	29.00 ± 10.42	44.57 ± 27.66	0.162

SEM: standard error of mean; RBC: red blood cell; WBC: white blood cell.

countries, respectively.[26] However, there are some challenges on their use, mostly on their ambiguous efficacy and safety. Therefore, there is an emerging need for evidence-based studies on their use.[27,28]

Despite several preclinical studies on antipyretic and antibacterial effects of rhubarb and its use in children with shigellosis, there was no clinical study on the effects of *R. ribes* on children's shigellosis. This study demonstrated that *R. ribes* syrup reduced the duration of diarrhea, fever and need for antipyretics.

In this study, both study arms received standard antibiotic treatment. Ceftriaxone is a good choice for antimicrobial therapy against *Shigella* infection, even in the case of multidrug resistance.[2,29] Additionally, oral cefixime is an approved option for children's shigellosis.[30,31] Thus, better outcomes in the arm of *R. ribes* group, relative to the placebo, could be attributed to the active ingredients of *R. ribes* fruit. Hence, *R. ribes* syrup can be prescribed as an adjuvant treatment for the management of shigellosis in pediatric patients. Yet, there is no evidence for choosing *R. ribes* as an alternative treatment (instead of antibiotic regimens).

There are scarce studies on herbal medicines for shigellosis in children. One of the most prominent clinical studies assessed the efficacy of green banana (GB), as a complementary treatment. This study showed significant improvement of stool characteristics (such as mucus and blood in stool), stool frequency and volume in children receiving GB. "Clinical success rates were 85% in GB group compared with 67% in controls."[1] However, GB is not native to many countries, including the Eastern Mediterranean Region. Also, GB should be eaten in a relatively high volume (i.e., 250 g/L); therefore, it may not be tolerated well by children with shigellosis.

There are no data on the exact mechanism of the action of *R. ribes* in children's shigellosis. Nevertheless, some plausible mechanisms exist which could be helpful for better understanding of its clinical effects.

Firstly, *R. ribes* possesses a wide range of antibacterial compounds, such as phenols and flavonoids.[32] Different parts of *R. ribes* have been investigated for their antibacterial activity against different pathogenic bacteria.[3,4,33–35] An *in vitro* study by Kazemi Darsanaki et al[5] revealed

a significant antibacterial activity of *R. ribes* against *Shigella*. There are several investigations regarding the major antibacterial constituents of *R. ribes*. Rhein is one of the most potent and often cited active substance against various bacteria.[36] Aloe emodin, chrysophanol, physcion and emodin, other important active ingredients of *R. ribes*, are also well-studied for their antibacterial activity.[33,37,38]

This antibacterial activity can occur through different mechanisms, such as "inhibition of enzymes in the mitochondrial electron transport system" and blockage of the inhibitory effect of the bacterial enzymes.[39] Also, disturbance of the efflux system may be made by the plant's active ingredients at the action locus.[40]

In addition, *R. ribes* is known as a potent anti-inflammatory agent.[41–43] It is notable that *Shigella*-related inflammatory response plays a significant role in the disease development and its symptoms.[44] Accordingly, using anti-inflammatory materials has proven to have a beneficial effect on infected humans.[45]

Along with the aforementioned implications, the antipyretic potential of *R. ribes* should be kept in mind as another important effect. Heat syndromes have been treated by applying cooling methods in several traditional medicines. Recently, there have been several investigations conducted on the antipyretic action and underlying explanations of cold-natured medicinal herbs. Emodin, as an important active ingredient of *R. ribes*, was found to alter the expression of the transient receptor potential (TRP) melastatin 8 (TRPM8) mRNA and TRP vanilloid 1 (TRPV1) mRNA through *in vitro* studies.[46,47] TRPV1 and TRPM8 are temperature-sensitive transient receptor potential channels, expressed in primary sensory neurons. Later, Kong and his colleagues,[48] in their work on Chinese rhubarb, suggested that the regulation of expression of TRPV1 and TRPM8 offers a potential explanation for antipyretic activity of this cold-natured plant. These findings may explain why Ribes syrup has good antipyretic effects on shigellosis in children; apart from its antimicrobial effects, it can significantly reduce the duration of fever and need for antipyretic treatment.

Finally, *R. ribes* syrup reduced the duration of diarrhea and frequency of defecation. In *Qanon*, Avicenna (980–1037 A.D.)[49] mentioned the antidiarrheal effects of rhubarb;[13] it is also one of the most cited Chinese herbal drugs.[50] In addition, it has been shown that tannin-related compounds in rhubarb have antidiarrheal effects.[51] A recent study on Siberian rhubarb revealed potent antioxidant properties in its petioles and stems. However, its roots had noticeable antimicrobial activity. Therefore, it seems that different members of rhubarb family can be similar in their activity against diarrhea.[52]

In brief, our research is in accordance with previous studies. Rhubarb is a potent antibacterial, anti-inflammatory, antioxidant[53] and antipyretic herb. Therefore, we expected that children with *Shigella* dysentery may benefit from *R. ribes* syrup.

Nonetheless, it seems that more scientific studies are needed to develop a mechanistic understanding on *R. ribes* efficacy for childhood shigellosis. Although its mechanisms of function are not understood, the syrup made from *R. ribes* fruit may be an available, natural, safe and efficient complementary treatment for children with shigellosis.

Assessment of *R. ribes* efficacy for treatment of other types of childhood diarrhea may be interesting for other researchers. It would be especially interesting to test its effects in the treatment of viral types of diarrhea which do not require antibiotic treatment.

In this study, we had some limitations. Firstly, our sample size was relatively small. However, this study was the first clinical trial on *R. ribes* syrup for shigellosis in children. Therefore, we preferred to adopt the standard required sample size. Also, we requested stool analysis at enrollment time, and then 2 and 5 days later. However, daily stool examination might enable us to make more a precise analysis of the antimicrobial effects of *R. ribes* syrup.

5 Conclusion

According to the findings of this investigation, *R. ribes* syrup, as a complementary treatment to standard antibiotic therapy, has a significant effect in alleviation of the severity of fever and diarrhea in children with *Shigella* dysentery. Also, it is efficient in reducing the duration of dysentery, fever and abdominal pain. Thus, it can be recommended as a complementary medicine for these patients. All in all, this research tried to move current knowledge forward by evaluation of traditional use of *R. ribes* for children with bloody diarrhea (especially *Shigella* dysentery) in a clinical trial. However, further studies with larger sample size and by resolving our shortcomings are recommended. Moreover, assessment of antidiarrheal effect of *R. ribes* in patients with noninfectious diarrhea is suggested.

6 Competing interests

The authors declare that they have no competing interests.

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