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Short-Communication

Ginger supplementation in children with oligoarticular juvenile idiopathic arthritis: A triple-blind randomized clinical trial

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Abstract

Objective: This study aimed to investigate the effect of ginger supplementation on treatment responses in children with oligoarticular juvenile idiopathic arthritis (oligo-JIA).

Materials and Methods: A total of forty children between the ages of 6 and 16 years with oligo-JIA were randomly assigned to receive either a ginger capsule (containing 250 mg of powdered *Zingiber officinale* rhizomes) or a placebo twice daily for three months, along with standard treatment. The response to therapy was measured using the American College of Rheumatology Pediatric 30, 50, 70, and 90 response criteria (ACR-Pedi 30, 50, 70, and 90) after three months of supplementation.

Results: ACR-Pedi 30, 50, 70, and 90 responses were significantly higher among those receiving ginger supplement ($p<0.001$, $p<0.001$, $p<0.001$, and $p=0.001$, respectively).

Conclusion: In this study, ginger supplementation improved ACR-Pedi 30, 50, 70 and 90 responses in pediatric patients with oligo-JIA. Given its safety profile and anti-inflammatory and immunomodulatory properties, ginger supplementation may enhance therapeutic responses in this clinical setting. However, due to certain limitations within our study, further research is essential to confirm these promising findings.

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Introduction

Juvenile idiopathic arthritis (JIA) is the most prevalent form of chronic inflammatory joint disease affecting children under the age of 16. It affects approximately one in every 1000 children (Al-Mayouf et al. 2021; Onel et al. 2022)). The primary clinical manifestation of JIA is

persistent joint inflammation resulting from the accumulation of synovial fluid and thickening of the synovial membrane. The synovial tissue becomes inflamed and hyperplastic due to excessive proliferation of synoviocytes and infiltration of various immune cells, particularly T-cells, B-cells, natural killer cells, macrophages, dendritic cells, plasma cells, and neutrophils. Additionally, the inflamed synovium secretes excess synovial fluid that contains inflammatory cells and cytokines. These changes can result in joint destruction and systemic complications (Zaripova et al. 2021).

JIA, as a heterogeneous disorder, is categorized into six subtypes: systemic arthritis, polyarthritis, oligoarthritis, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis (Onel et al. 2022; Petty et al. 2004). This classification is based on the pattern of joint involvement, extra-articular symptoms and systemic features (Table 1) (Petty et al. 2004; Zaripova et al. 2021). Among these, oligoarticular JIA (oligo-JIA) is the most common, representing for approximately 50% of all cases (Onel et al. 2022). According to the criteria stablished by the American College of Rheumatology (ACR) and the International League of Associations for Rheumatology (ILAR), oligo-JIA is defined as the presence of arthritis in up to four joints. It typically affects large joints, predominantly knees and ankles, in an asymmetrical pattern (Onel et al. 2022; Petty et al. 2004).

The purpose of this study was to evaluate the potential effect of ginger supplementation on treatment responses in children with oligo-JIA.

Table 1. JIA classification categories (Onel et al. 2022; Petty et al. 2004; Zaripova et al. 2021)

Subtype	**Diagnostic criteria**	
	Arthritis	**Extra-articular manifestations and systemic features**
Systemic arthritis	Presence of arthritis in one or more joints	Fever of at least 2 weeks duration (daily for at least 3 days) and At least one of the following findings: 1. Evanescent 2. Erythematous rash 3. Hepatomegaly or splenomegaly 4. Lymph node enlargement 5. Serositis
Polyarthritis	Presence of arthritis in five or more joints	This subtype is further divided according to the presence or absence of RF: 1. Polyarthritis RF negative 2. Polyarthritis RF positive
Oligoarthritis	Presence of arthritis in one to four joints during the first 6 months This subtype is further divided to two subclasses: 1. persistent (children with one to four joints throughout the disease course) 2. Extended (children with five or more joints after first 6 months)	
Enthesitis-related arthritis	Presence of arthritis and enthesitis, or arthritis alone, or enthesitis alone	Two or more of the following: 1. Sacroiliac joint tenderness 2. Lumbosacral inflammatory pain 3. Positive HLA-B27 4. First-degree relative with acute anterior uveitis 5. Ankylosing spondylitis 6. Inflammatory bowel disease with sacroiliitis 7. Reactive arthritis 8. Acute anterior uveitis 9. Onset of arthritis in males >6 years of age
Psoriatic arthritis	Presence of arthritis	Two or more of the following: 1. Psoriasis in a first-degree relative 2. Dactylitis 3. Appropriate fingernail abnormalities (eg, pitting or onycholysis)
Undifferentiated arthritis	Presence of arthritis that either does not fulfill one of the above categories due to incomplete features or meets the criteria for more than one category	-

RF, rheumatoid factor; HLA, human leukocyte antigen

Materials and Methods

Study design

This triple-blind, placebo-controlled, randomized clinical trial was conducted in the rheumatology clinic of Akbar Hospital, a tertiary referral teaching hospital affiliated to Mashhad University of Medical Sciences between March 2022 and March 2024.

Ethical considerations

The study received approval from the Institutional Review Board and Ethics Committee of Mashhad University of Medical Sciences in Mashhad, Iran (approval code: IR.MUMS.REC.1399.460). Additionally, it was registered as a clinical trial on December 8, 2021, with the Iranian Registry of Clinical Trials (http://www.irct.ir), under the identification number IRCT20191221045837N4.

Study protocol

Children aged 6-16 years with diagnosis of oligo-JIA who were referred to the rheumatology clinic were recruited. The diagnosis was established in accordance with the ACR guideline (Onel et al. 2022). Patients (or their parents) who declined to provide research authorization, as well as individuals with diabetes mellitus (HbA1C >6.5 g/dl), medical history of cardiovascular, renal, gastrointestinal, hepatic, biliary or other rheumatic disorders (except for JIA), or recent (within the past three months) or ongoing use of ginger or other herbal supplements were not included to the study. Patients who did not complete the follow-up were excluded from the study. Parents were asked to supervise the child's correct use of the medication, and this supervision was evaluated by the pharmacist during the study.

Eligible children were randomly assigned to receive either ginger supplement or placebo. All participants received standard medical management for oligo-JIA during the study. The intervention group received a ginger capsule (containing 250 mg of powdered *Z. officinale* rhizomes) twice daily for three months. The control group received placebo capsules identical in appearance and quantity. These capsules were prepared by Gol Daru Pharmaceutical Company (Isfahan, Iran) in 2022. The content of capsules was authenticated through High-Performance Liquid Chromatography (HPLC) analysis, based on gingerol content, by the Department of Pharmacognosy at Mashhad University of Medical Science.

Randomization and blinding

We used the permuted block randomization method (block size of four) to ensure balanced allocation of patients to each group. A computer-generated list of random allocation sequences was prepared. To maintain blinding, both ginger and placebo capsules were produced in a way to look identical and were similarly packaged, labeled as A and B respectively (produced by Gol Daru Pharmaceutical Company). Included patients received their capsules (labeled A or B) according to the allocation sequence. Patient evaluations during treatment were conducted by a pediatric rheumatologist and a pharmacy student, both of whom were unaware of the patients' group assignments.

Sample size

Given the lack of clinical trials exploring the anti-inflammatory properties of ginger in patients with Oligo-JIA, this research was designed as a pilot study. The sample size was estimated at 20 participants, based on the non-central t-distribution (NCT) method and following the rules of thumb, aiming for an 80% statistical power, a standardized effect size of 0.2, and a significance level of $p < 0.05$ for each treatment group (Whitehead et al. 2016).

Patient assessment and data collection

The demographic characteristics of the patients, including sex, age, and weight, as

well as the severity of the disease (both at baseline and three months later), possible side effects, and concurrent medications were recorded. The ACR-Pedi 30 response was considered the primary outcome. Secondary outcomes involved ACR-Pedi 50, 70 and 90 responses and adverse events.

The ACR-Pedi 30, 50, 70 and 90 criteria, which are valid assessment tools, have demonstrated high sensitivity (100%) and specificity (85%) in defining disease improvement (Consolaro et al. 2016; Trincianti et al. 2021). As a result, we employed these criteria to evaluate patient responses to therapy in our study. An ACR-Pedi 30 response is characterized by a minimum of 30% improvement in at least three of the six core disease measures from baseline, without more than one variable worsening by over 30%. The core criteria include: 1. Physician global assessment of disease activity (measured using a 0-10 cm Visual Analogue Scale [VAS], with 0 representing the best score); 2. Patient/parent overall assessment of well-being (also based on a 0-10 cm VAS); 3. Functional ability; 4. Number of joints with active arthritis; 5. Number of joints with limited range of motion (ROM); and 6. Erythrocyte sedimentation rate (ESR) level (measured by the Westergren method). Similarly, ACR-Pedi 50, 70 and 90 responses are defined as achieving at least 50%, 70% and 90% improvement, respectively, in at least three of these core variables, with no more than one variable worsening by over 30% (Consolaro et al. 2016; Trincianti et al. 2021).

Throughout the study, patients were closely monitored for the occurrence of any adverse events. When an adverse reaction was suspected, the Naranjo Adverse Drug Reaction Probability Scale was applied to determine the likelihood of a causal relationship.

Statistical analyses

All statistical analyses were performed using SPSS Statistics for Windows, version 22. Analyses adhered to the intention-to-treat (ITT) approach. The Kolmogorov-Smirnov test assessed the normality of continuous variable distributions. Continuous data are presented as means with standard deviations (SD) or medians with interquartile ranges [IQR], depending on distribution. Categorical data are expressed as counts and percentages. To compare continuous variables, either the independent samples t-test or the Mann-Whitney U test was used, based on data distribution. Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test. A *p*-value less than 0.05 was deemed statistically significant.

Results

Out of 180 children initially screened, only 40 patients met the inclusion criteria and participated in the study. These participants were randomly divided into two groups: one receiving a ginger supplement and the other a placebo, both in addition to the standard treatment for oligo-JIA. During the trial, two children withdrew due to mild skin rashes (one from each group). Ultimately, 38 children completed the study as shown in Figure 1. The average age of the participants was 10.32 years (SD = 2.94), with 20 of them (50%) being male. Table 2 provides a summary of their demographic data and initial medical management, revealing no significant differences between two groups.

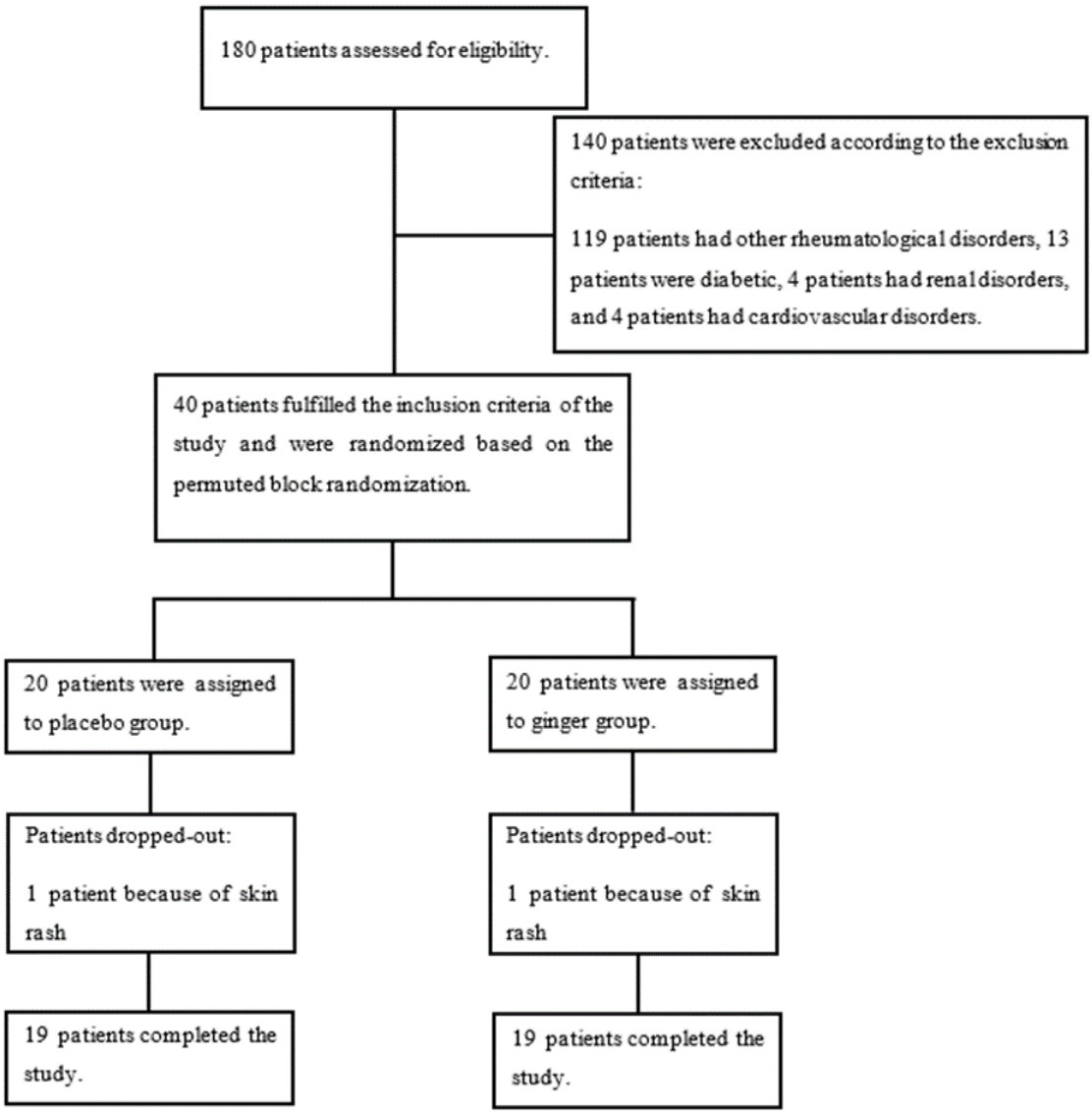

Figure 1. Consort flow chart of the study

Table 2. Demographic characteristics of patients and their initial medical management

Variable, Mean (SD) or n (%)	Placebo group (n = 20)	Ginger group (n = 20)	p-value
Age, years	10.65 (3.01)	10 (2.91)	0.49[a]
		Sex	
Male	8 (40)	12 (60)	0.34[b]
Female	12 (60)	8 (40)	
Weight, kg	29.6 (1.26)	28.2 (1.51)	0.26[a]
		Initial medical management of oligo-JIA*	
Methotrexate dose (mg/weak)	14.2 (1.58)	14.1 (1.26)	0.16[a]
Naproxen dose (mg/day)	420.8 (3.25)	421 (2.87)	0.26[a]
Prednisolone dose (mg/day)	13.9 (1.98)	13.6 (1.69)	0.14[a]

*All included patients received standard medical management of oligo-JIA according to the ACR guideline. [a] independent samples t-test. [b]$\chi 2$ test

Throughout the study, we monitored clinical symptoms and laboratory parameters, with the findings detailed in Table 3. After three months, all core criteria of the ACR-Pedi responses showed significant improvement in the ginger group. Finally, the ACR-Pedi 30, 50, 70 and 90 responses were measured and compared between the groups. As shown in Table 4, the ACR-Pedi 30, 50, 70 and 90 responses were substantially higher in the ginger group ($p<0.001$, $p<0.001$, $p<0.001$, and $p=0.001$, respectively).

Both groups tolerated the treatment effectively, with no serious adverse reactions reported. Only two participants (one from each group) developed mild skin rashes localized to the chest and face. Overall, the incidence of side effects was not significantly different between the groups ($p = 0.55$). We assessed the Narenjo score for both patients, which ranged from 2 to 4. This suggests a low possibility that the rashes were caused by the trial medications. Given that these skin reactions were mild and occurred in only one patient within each group, and considering the Narenjo score, our findings demonstrate that daily intake of 500 mg of ginger powder over three months is safe for children aged 6-16 years old.

Table 3. Changes in clinical findings and laboratory markers of patients during the study period in the two groups

Variable, Median [IQR]	Placebo group		Ginger group		p-value
	Baseline (n = 20)	After three months (n = 19)	Baseline (n = 20)	After three months (n = 19)	
Physician global assessment	4 [4-5.75]	4 [3-5]	5 [4-6.75]	1 [0.0-1]	<0.001[a]
Patient/parent global assessment	4.5 [4-5]	4 [3-5]	5 [4-6]	0.0 [0.0-1]	<0.001[a]
Functional ability	1.33 [1.33-1.92]	1.33 [1.33-2.33]	2.33 [1.67-3.25]	1 [0.33-1.33]	0.001[a]
Number of joints with active arthritis	1 [1-2]	1 [1-2]	1 [1-2]	0.0 [0.0-1]	<0.001[a]
Number of joints with reduced ROM	1 [1-1]	1 [1-2]	1 [1-2]	0.0 [0.0-1]	0.01[a]
ESR level, mm/hr	7 [4.25-14.5]	14 [10-23]	18.5 [10.25- 43.5]	4 [2-15]	0.003[a]

ESR, erythrocyte sedimentation rate; IQR, interquartile range; ROM, range of motion. [a]Mann-Whitney U test

Table 4. ACR-Pedi 30, 50, 70, and 90 responses of patients after 3 months

ACR-Pedi Response - n (%)	Placebo group (n = 19)	Ginger group (n = 19)	p-value
ACR-Pedi 30*	1 (5.3)	18 (94.7)	<0.001[a]
ACR-Pedi 50*	0	18 (94.7)	<0.001[a]
ACR-Pedi 70*	0	15 (78.9)	<0.001[a]
ACR-Pedi 90*	0	9 (47.4)	0.001[a]

*An ACR-Pedi 30 response is characterized by a minimum of 30% improvement in at least three of the six core disease measures from baseline, without more than one variable worsening by over 30%. The core criteria include 1. Physician global assessment of disease activity (measured using a 0-10 cm Visual Analogue Scale [VAS], with 0 representing the best score); 2. Patient/parent overall assessment of well-being (also based on a 0-10 cm VAS); 3. Functional ability; 4. Number of joints with active arthritis; 5. Number of joints with limited range of motion (ROM); and 6. Erythrocyte sedimentation rate (ESR) level. Similarly, ACR-Pedi 50, 70 and 90 responses are defined as achieving at least 50%, 70% and 90% improvement, respectively, in at least three of these core variables, with no more than one variable worsening by over 30%. [a]$\chi 2$ test

Discussion

Based on the findings of this study, ginger supplementation (one capsule containing 250 mg of ginger powder twice daily for three months), along with standard treatment for oligo-JIA, improved both clinical manifestations and laboratory markers of the disease in children. Additionally, children receiving ginger

showed significantly higher ACR-Pedi 30, 50, 70 and 90 responses.

Ginger has long been used to prevent and alleviate nausea and vomiting in pediatric populations (Dupuis and Nathan 2003; Essawy et al. 2021; Ladas et al. 2006; Nocerino et al. 2021; Quimby 2007). Its anti-emetic properties are mainly attributed to bioactive compounds such as 6-, 8-, and 10-gingerol, as well as 6-shogaol. These compounds possess anti-inflammatory and anti-oxidant properties, which help reduce nausea and vomiting by lowering serotonin (5-HT) levels, blocking 5-HT3 and muscarinic M3 receptors, and modulating gastrointestinal motility (Dai et al. 2022; Hu et al. 2016; Nocerino et al. 2021). Additionally, ginger has been employed in the management of recurrent abdominal pain in children due to its anti-spasmodic effects on visceral smooth muscles (Weydert 2018). Overall, ginger has been shown to be safe and effective as both an anti-emetic and anti-spasmodic agent in children, with doses of up to 1000 mg per day (Essawy et al. 2021; Pillai et al. 2011; Weydert 2018). In this study, ginger was prescribed at a daily dose of 500 mg, due to its established safety profile in children. It was well tolerated over a three-month period, with no serious adverse effects reported.

Although no studies have evaluated the effectiveness of ginger supplementation in pediatric rheumatic disorders, its efficacy has been investigated in adults with inflammatory rheumatic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA) (Altman and Marcussen 2001; Aryaeian et al. 2019a; Aryaeian et al. 2019b; Rondanelli et al. 2020).

A comprehensive investigation involving 247 patients with OA found that ginger supplementation significantly alleviated pain intensity, reduced morning stiffness, improved ROM in affected joints, and enhanced daily activities, sports performance, and overall quality of life. During this study, patients received one capsule of ginger extract (255 mg) twice daily for 6 weeks (Altman and Marcussen 2001). Another research on 120 patients with OA revealed that ginger supplementation (two capsules of 500 mg powdered ginger daily over three months) was associated with a decline in inflammatory markers including IL-1, TNF-α, C-reactive protein (CRP), and nitric oxide (NO) (Mozaffari-Khosravi et al. 2016; Naderi et al. 2016).

In a trial involving 66 patients with RA, ginger consumption (two capsules of 750 mg powdered ginger daily for 3 months) led to improved clinical symptoms and disease activity, evaluated through the Disease Activity Score-28 (DAS-28) (Aryaeian et al. 2019a; Aryaeian et al. 2019b). Ginger significantly increased the expression of forkhead box P3 (FoxP3) and peroxisome proliferator-activated receptor-gamma (PPAR-γ) genes (Aryaeian et al. 2019b). These factors are associated with the maintenance of immunological tolerance (Goyal et al. 2018; Liu et al. 2016; Lu et al. 2017). Additionally, ginger supplementation led to a significant reduction in the expression of T-box transcription factor TBX (T-bet) and RAR-related orphan receptor γt (RORγt) genes (Aryaeian et al. 2019b). These factors play a key role in the pathogenesis of many inflammatory and autoimmune disorders (Ji et al. 2011; Tan et al. 2020).

The anti-inflammatory properties of ginger are attributed to the reduction of inflammatory factors including high-sensitivity CRP (hs-CRP), TNF-α, IL-2 and IL-1β and enhancement of anti-inflammatory cytokines such as IL-10 (Aryaeian et al. 2019a; Zhang et al. 2016). Ginger also suppresses the biosynthesis of prostaglandins and leukotrienes by inhibiting the enzymes COX-2 and lipoxygenase (Grzanna et al. 2005).

Ginger inhibits the migration of monocytes and leukocytes by reducing the production of key chemokines such as monocyte chemoattractant protein-1 (MCP-1) and RANTES (regulated upon activation, normal T cell expressed and

secreted). Also, it inhibits the activation of macrophages and neutrophils (Ezzat et al. 2018).

Ginger improves the inflammatory state by targeting various signaling pathways including NF-κB, signal transducer and activator of transcription (STAT), mammalian target of rapamycin (mTOR), toll-like receptors (TLRs), NOD-, LRR- and pyrin domain-containing proteins (NLRPs), and mitogen-activated protein kinase (MAPK). This leads to a decrease in the gene expression of inflammatory cytokines (Roudsari et al. 2021).

The interpretation of our findings needs to be considered alongside the following limitations. This study was single-centered and was performed on a small number of patients. We did not measure serum cytokine levels due to financial constraints. Another important limitation is the short duration of ginger supplementation (only three months), which may have been insufficient to achieve maximal efficacy or to detect side effects following chronic use.

In the present study, ginger supplementation improved ACR-Pedi 30, 50, 70 and 90 responses in pediatric patients with oligo-JIA. Regarding the safety, anti-inflammatory and immunomodulatory properties of ginger, it seems that ginger supplementation, along with standard treatment of oligo-JIA, may enhance clinical outcomes and therapeutic responses. However, due to limitations of our study, further research is needed to confirm our findings.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors participated in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Study conception and design: ZH, AA, AM, MOB. Acquisition of data: ZH, MAB, AM, HSS. Analysis and interpretation of data: ZH, AM. Statistical Analysis: ZAS.

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