Original Article

Effectiveness of hydroalcoholic extract of *Nasturtium Officinale* on sleep quality, asthma control and quality of life in asthmatic patients: a randomized controlled trial

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ABSTRACT

Objectives: Considering the role of oxidants in asthma, airway inflammation, and the anti-inflammatory effects of *Nasturtium officinale* extract, this study aimed to investigate the impact of the hydroalcoholic extract of *Nasturtium officinale* on sleep quality, asthma control, and quality of life in asthmatic patients.

Methods: This parallel group randomized clinical trial was conducted in Yasuj, Iran. It included 60 patients who randomly received either *Nasturtium officinale* hydroalcoholic extract (500 mg daily, for four weeks, orally plus routine care) or a placebo (500 mg capsule containing flour daily, for four weeks, orally plus routine care). To achieve the study objectives, lung function (FEV1, FVC, PEF, FEF 25-75%, and FEV1/FVC), quality of life as measured by the 12-item Short Form Health Survey (SF-12), sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI), and asthma control as examined by the Asthma Control Test (ACT) were assessed at baseline and one-month follow-up.

Results: In total, 48 patients (22 patients in the intervention group and 26 patients in the control group) completed the study. The analyses showed no significant differences between the two groups regarding changes in lung function, quality of life, sleep quality, and status of asthma control within a one-month follow-up.

Conclusion: The findings suggest that the hydroalcoholic extract of Nasturtium Officinale does not appear to improve sleep quality, asthma control, and quality of life in asthmatic patients in the short term.

Keywords: asthma, quality of sleep, asthma control, quality of life, Nasturtium officinale

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Introduction

Asthma is a chronic disease of the upper respiratory tract that arises due to bronchial hyper-inflammation and an airway hyper-responsive reaction. A significant number of patients suffer from uncontrolled asthma, which is characterized by reversible obstruction and stenosis, severe response, intense inflammation, and altered airway structure. These changes are mediated by inflammatory mediators, including cytokines (chemokines, interleukins), and lipid mediators (leukotrienes and prostaglandins), which are produced by inflammatory cells, including T cells, eosinophils, mast cells, basophils, and non-inflammatory cells such as fibroblasts (1).

Patients with asthma are at a higher risk of asthma-associated mortality and hospitalization, experiencing significant impairments in their quality of life (QOL) (2). Individuals with asthma are less likely to report excellent health compared to those without the condition. Asthma ranks fourth, after cancer and kidney disease, in the list of diseases that compel people to take time off from work, school, or study (3). Moreover, patients with asthma often experience comorbidities such as rhinitis, obesity, and cardiovascular disease (4). Therefore, international guidelines for asthma therapies aim to achieve and maintain long-term control of the disease, improve the QOL of the patient by minimizing symptoms, and enhance physical, psychological, and social function. Indeed, improvements in health-related QOL (HR-QOL) may be more indicative of treatment success compared to physiological endpoints such as spirometric measures of lung function (5). However, despite the treatment strategies indicated by international guidelines, at least 40% of patients have symptomatic or poorly controlled disease, while the extensive use of low-dose inhaled corticosteroids as a first-line treatment results in severe side effects such as mouth infections, cataracts, and osteoporosis (6-8). As a result, the exploration of new therapeutic avenues with limited adverse effects for the treatment of chronic asthma is imperative. In addition, several randomized clinical trials have been conducted to assess the effectiveness and safety of combination therapies in human populations suffering from asthma (9, 10). In this respect, many patients with chronic allergic conditions seek complementary and alternative medicine therapies, including traditional Chinese medicines. This trend has begun to attract interest from mainstream healthcare providers and scientific investigators (11, 12). *Nasturtium officinale*, known as Watercress, is a species of aquatic plant belonging to the cabbage family (Brassicaceae) that generally grows in cold, clear water (13). *Nasturtium officinale* contains vitamins A, B, C, and E, folic acid, and high concentrations of glucosinolates as well as carotenoids such as B carotene, lutein, and quercetin, which contain elements such as iodine, chromium, iron, calcium, and sulfur (14, 15). The folk medicinal application of *Nasturtium officinale* for the treatment of diabetes, bronchitis, diuresis, and influenza has been reported (13). The high antioxidant activity of the *Nasturtium officinale* extract has been attributed to a variety of mechanisms and reactions, including inhibition of lipid peroxidation, prevention of hydrogen accumulation, and radical scavenging (16).

There are very limited data available in the local and regional settings to assess the impact of herbal medicine on sleep quality, asthma control, and quality of life (QOL). Considering the role of oxidants in asthma and airway inflammation, and the antioxidant and anti-inflammatory effects of *Nasturtium officinale* extract, this study, for the first time, attempted to investigate the impact of the hydroalcoholic extract of *Nasturtium* officinale on sleep quality, asthma control, and QOL in asthmatic patients.

Methods

Design and data collection

This was a parallel group randomized trial. The study was conducted from 2020 to 2022 and was approved by the ethics committee of Yasuj Medical University, Yasuj, Iran. This study was a single randomized clinical trial undertaken in the Mofateh clinic, Yasuj, Iran. A blinding method was used so that the patients were not aware of their allocations to study groups, and all medications were placed into identical capsules in terms of size, shape, and color by the pharmacist.

Allocation to the *Nasturtium officinale* (Group A) or placebo groups (Group B) was done by the "block" randomization method. Randomization tools were used as statistical software, and the concealment method was done by placing envelopes in the packages.

The following formula was used to calculate the sample size (Benjamin et al., 2004 (17)). As such, the assignment of at least 30 individuals was estimated for each group; where α=0.05; β=0.80; P1= Ratio of those who stopped inhaled asthma treatment in the intervention group i.e., pycnogenol1 herbal treatment: 0.1%; P2= Ratio of those who stopped asthma inhalation therapy in the placebo group: 0.4%.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \left[P_1(1-P_1) + P_2(1-P_2)\right]}{(P_1 - P_2)^2}$$

Inclusion criteria

1. Adult male or female patients (age 18 to 65 years)
2. Asthma diagnosis based on GINA guidelines (Global Initiative for Asthma, 2014 (18))
3. Having a score of 5-24 on the Asthma Control Test

Figure 1: Nasturtium officinale

(ACT) with uncontrolled asthma symptoms (18, 19)
4. No worsening of asthma in the last four weeks
5. Complete informed consent

The exclusion criteria included a history of smoking, pregnancy, any underlying disease (heart, kidney, neurology, psychiatry, etc.), consumption of any combination containing Nasturtium officinale, and unwillingness to participate in the study.

Description of intervention for both groups

The stems and leaves of *Nasturtium officinale* were collected in September 2020 from the Kakan region located in Yasuj, Iran (Figure 1) and were identified by a botanist, Dr. Jafari. A voucher specimen (Herbarium no. HYU30230) was deposited in Yasuj University. After collection, they were cleaned, shade dried, and powdered. A hundred grams of the pulverized plant material was soaked with 1 L of ethanol (70%, Yasan, Iran). The extraction was performed *via* maceration in an incubator at 37 °C for 48 hours. After the filtration process, it was subsequently concentrated under reduced pressure using a Rotavapor (Heidolph, Germany) at 40 °C. The dried extract was stored in a refrigerator at –20 °C until further experiments (20).

Nasturtium officinale hydroalcoholic extract was administered as below:

Group A: The Nasturtium officinale hydroalcoholic extract was administered in the form of a capsule (500 mg daily for four weeks, orally).

Group B (placebo group): A capsule containing flour was administered (500 mg daily for four weeks, orally).

Both groups received routine care, including Salbutamol, Salmeterol or Formoterol, Budesonide or Fluticasone, and Montelukast, according to the GINA 2014 guidelines (Global Initiative for Asthma Strategy).

Outcomes

The primary outcome of this study was the quality of sleep and Quality of Life (QOL). The secondary outcome was the effect of the intervention on asthma control and lung function, as determined by spirometry.

Measures

In addition to collecting information on age, gender, occupation, and BMI, the following measures were used:

1. Pittsburgh Sleep Quality Index (PSQI): This self-report scale was used for the assessment of the quality of sleep. It consists of several fields including sleep latency, subjective sleep quality, sleep duration, habitual sleep efficacy, sleep disturbance, use of sleep medication, and daytime dysfunction. Most of the questions are multiple-choice, short, and easy to understand. The answers are graded from 0-3, and the total score ranges from 0-21. A higher score indicates a higher sleep disorder (21). The validity and reliability of the questionnaire are approved (22).

2. 12-item Short Form Health Survey (SF-12): This questionnaire was used to evaluate Quality of Life (QOL), which includes 12 questions with eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Scoring uses the RAND system from zero to 100. The score of each domain is obtained by aggregating the question scores in every domain and dividing the yielded number by the number of questions in the same domain. A higher score indicates better quality of life (23). The validity and reliability of the questionnaire are approved (24).

3. Asthma Control Test (ACT): This numerical score is used to assess the control of asthma (25). It includes five questions on patient-related asthma control aspects. The ACT assesses the frequency of shortness of breath, night/early awakening, use of life-saving medications, overall asthma control, and decreased productivity. Each question is answered on a 5-point scale, with a total score

ranging from 5 to 25; higher scores indicate improved asthma control (25, 26). A score of ≥20 indicates "well-controlled" asthma, while a score of <20 indicates "not well-controlled" asthma. The validity and reliability of the questionnaire have been confirmed (27).

4. Adverse effects: The patients in both groups were asked to record any adverse effects in their diary during the treatment. Adverse effects were mapped to preferred terms and body systems and coded using the Adverse Reaction Terminology Dictionary of the World Health Organization (28).

5. Lung Function Tests: The pulmonary function test was performed using a spirometer (RESMED3VPAP), according to the standards outlined by the ATS/ERS Task Force (29). Forced vital capacity (FVC), forced expiratory flow between 25 and 75% (FEF 25-75%), mean peak expiratory flow (PEF), and forced expiratory volume in one second in liters (FEV1) and the relation (FEV1/FVC) were recorded.

All questionnaires (including ACT, QOL, and PSQI) were completed at baseline and one-month follow-up.

Data analysis

Data were analyzed using descriptive statistics, including frequency, percent, median, and IQR. The Mann-Whitney U test and Chi-square (x2) test were used for comparisons between groups. As there were no missing values, no missing imputation technique was employed. The statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 21; SPSS, Chicago, IL. The significance level (p-value) was set at 0.05 for all analyses.

Results

Sample characteristics

The allocation of participants from 2020 to 2022 is depicted in Figure 2. As demonstrated in Table 1, there is no statistically significant difference in terms of age, gender, education, occupation, WHR, and BMI among the groups.

Comparison of Status of asthma control between Two Groups

No significant difference was detected between the groups in terms of asthma control status before and after the intervention (P>0.05) (Table 2). The *Nasturtium officinale* group demonstrated similar effects in

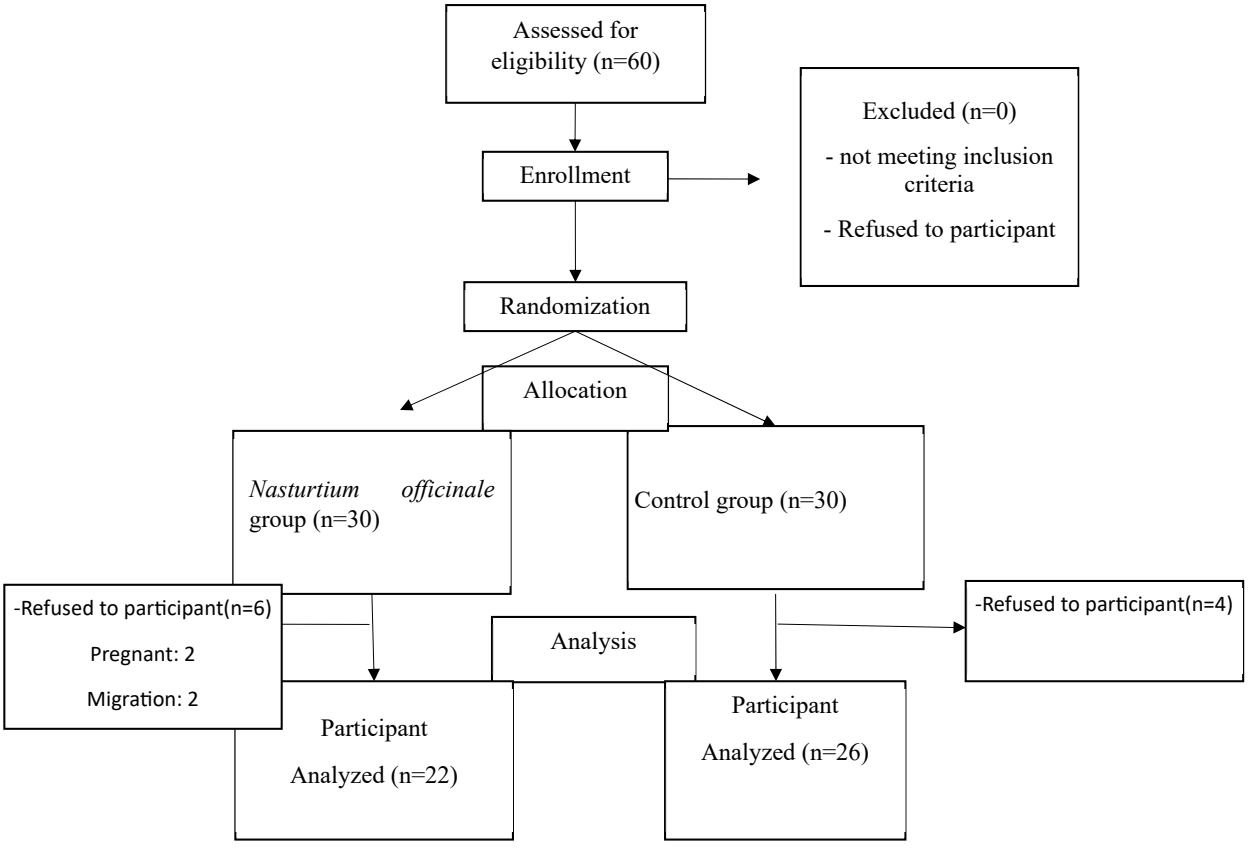

Figure 2: study flow diagram

Table 1: Characteristics of participants

variable *	Before			After		
	Intervention group (n=22)	Control group (n=26)	P value	Intervention group (n=22)	Control group (n=26)	P value
ACT score€	15 (11-18)	15.50 (12-19)	0.35	18 (13.75-19)	16 (13-19)	0.43

* n (%); x^2
** Median (IQR); Whitney test

Table 2: Status of asthma control

Variables		Intervention group (n=22)	Control group (n=26)	P value
Gender *	Male	11(50)	20(38.5)	0.51
	Female	11(50)	16(61.5)	
Education*	Guidance school or less	3(13.6)	2(7.7)	0.46
	Completed high school	14(636.6)	20(76.4)	
	College	5(22.7)	4(15.3)	
**Age (years) ** **		33.5(29.50-38.50)	32.50(30-39.25)	0.64
Married*	yes	6(27.3)	10(38.5)	0.42
	no	16(72.7)	16(61.5)	
**BMI (kg/m2) ** **		30.40(26.48-37.68)	28.17(24.69-42.16)	0.52
WHR**		0.82(0.78-0.86)	0.83(0.78-0.87)	0.46

*Median (IQR); Whitney test
€ACT: Asthma Control Test

Table 3: comparison of lung function

variable *	Before			After		
	Intervention group (n=22)	Control group (n=26)	P value	Intervention group (n=22)	Control group (n=26)	P value
FEV1	87(72.75-99.75)	82.50(71.50-103.25)	0.97	86(77.50-95.50)	121.50(69.25-93.25)	0.45
FVC	77(65.25-87.50)	73(66-92.50)	0.72	79.50(74.75-85.75)	77(69-88.75)	0.50
FEV1/FCV	119.50(114-122.25)	119(111-121)	0.56	113.50(109-120)	114(109-119.25)	0.95
PEF	83(68.75-98.75)	82.50(75-95)	0.85	90(73-102.75)	94(73-101.50)	0.84
FEF 25-75%	96.50(82.75-113.50)	105.50(88.75-125)	0.32	117.50(96.75-125.50)	114(85.25-137.75)	0.81

*Median (IQR); Whitney test

controlling asthma compared to the placebo group.

Comparison of Lung Function between Two Groups

The lung function, as indicated by the predicted FEV1, FVC, PEF, FEF 25-75%, and FEV1/FVC, was similar after one month of intervention with *Nasturtium officinale,* compared to the placebo group (P>0.05) (Table 3).

Comparison of quality of sleep and quality of life between Two Groups

After one month, the findings of the present study indicated that the *Nasturtium officinale* group scored similarly in all dimensions of the Pittsburgh Sleep Quality Index (PSQI) compared to the placebo group (P>0.05) (Table 4).

Moreover, according to the results presented in Table 4, no significant differences were observed between the groups in terms of Quality of Life (QOL) scores across all domains before the intervention (P>0.05). After one month, no statistically significant difference was identified in the QOL scores between the placebo group and the *Nasturtium officinale* group (P>0.05).

Comparison of adverse events between Two Groups

Table 4: comparison of sleep quality and quality of life

Variable*		Before			After		
		Intervention group (n=22)	Control group (n=26)	P value	Intervention group (n=22)	Control group (n=26)	P value
Quality of life**	PF	50(18.75-56.25)	50(25-100)	0.17	50(50-81.25)	50(50-100)	0.74
	RF	50(25-75)	62.50(50-75)	0.16	62(50-75)	62.50(50-75)	0.82
	RE	75(50-75)	67.75(46.87-100)	0.96	75(50-90.25)	75(37.50-100)	0.94
	VE	50(50-75)	75(43.75-81.25)	0.79	75(50-75)	75(50-100)	0.94
	SF	87.5(59.37-90.62)	75(50-100)	0.54	81.25(62.50-90.62)	87.50(59.37-100)	0.80
	BP	62.50(43.75-75)	50(43.75-81.25)	0.80	75(50-81.25)	75(50-100)	0.72
	GH	50(25-56.25)	25(25-50)	0.15	25(0-50)	25(0-25)	0.61
	MH	50(25-50)	25(25-50)	0.50	50(50-56.25)	50(25-50)	0.08
	Total score	57.81(51.17-64.06)	60.93(45.31-71.87)	0.57	62.50(54.87-70.31)	64.84(46.48-75)	0.69
Quality of sleep ¥	Component 1: Subjective sleep quality	1(1-2)	1(1-1)	0.10	1(1-1)	1(1-1)	-
	Component 2: Sleep latency	1(0.75-2)	1(1-2)	0.27	1(1-1)	1(1-1)	-
	Component 3: Sleep duration	0(0)	1(0.75-1)	0.06	0(0)	1(0-1)	0.06
	Component 4: Habitual sleep efficacy	0(0)	1(0.75-1)	0.07	0(0)	0(0-1)	0.13
	Component 5: Sleep disturbance	1(1-1)	3(1.75-4)	0.35	3(1.75-4)	3(2-5.25)	0.41
	Component 6: Use of sleep medication	0(0)	0(0)	-	0(0)	0(0)	-
	Component 7: Day time dysfunction	1(1-1)	1(1-2)	0.08	1(1-1)	1(1-2)	0.33
	Global score	6.50(4.75-8)	7(5.75-8)	0.25	7(6-9.25)	9(5-12)	0.34

*Median (IQR); Whitney test
** Physical functioning (21), role limitations due to physical problems (48), bodily pain (BP), general health perception (GH), social functioning (SF), role limitations due to emotional problems (RE), vitality (VT), and mental health (MH).
¥ Pittersberch sleep quality index (PSQI) score

The adverse effects reported for both *Nasturtium officinale* and placebo groups were all classified as mild. These effects did not result in any withdrawal from the trial. All the symptoms disappeared spontaneously without intervention.

Discussion

Asthma is a common chronic inflammatory disease. Herbal medicines, combined with routine pharmacotherapies, have been used in some previous studies for the treatment of asthma. The integrated approach improved outcomes more than pharmacotherapies alone. To date, few studies have investigated the effects of *Nasturtium officinale* on asthma, especially on the Quality of Life (QOL) of asthma patients. However, the protective effects of *Nasturtium officinale* have been proven in many conditions such as anti-inflammatory, anti-diabetic, anti-allergic, antibacterial, and anticancer herbal remedy, which has led to beneficial effects on the reproductive system (14, 30).

International guidelines state that treatments should not only improve the clinical status of asthma, thereby reducing the risk of exacerbations and possibly airway remodeling, but should also enable patients to feel and function better in their day-to-day lives (31). Only one study reported a QOL outcome, which showed that herbal medicine, along with pharmacotherapy, was not different from pharmacotherapy alone (32). Although the asthma quality of life outcome has been part of some studies investigating the effect of high-dose-inhaled glucocorticoids or exercise training on QOL in patients with asthma (33, 34), it has seldom been evaluated in studies with herbal medicines.

Moreover, asthma control is a clinical issue with many contributing factors. Aside from disease severity or resistance to treatment, poor asthma control may also be due to poor adherence, poor inhalation technique, and a patient's knowledge and attitudes (35). Quality of sleep may be an important factor affecting asthma control. Sleep disturbances, such as difficulty initiating and maintaining sleep and early morning awakenings, are commonly reported by patients with asthma (36, 37). Poor sleep condition has a detrimental impact on daily functioning and QOL, even in healthy people.

Within a one-month course, it was found that there were no significant differences in the effects of *Nasturtium officinale* hydroalcoholic extract supplementation on quality of sleep or QOL, nor on asthma control or lung function.

Our findings contrast with previous studies on the effect of *Nasturtium officinale* on asthma control. These studies reported the antinociceptive and antioxidant properties of the hydroalcoholic extract and chemical constituents of this plant. A study conducted by Gill CIR et al. on healthy individuals examined the effect of *Nasturtium officinale* on reducing lymphocyte DNA damage and altering the antioxidant status of blood. They concluded that watercress is associated with a reduced risk of cancer by reducing DNA damage and balancing the anti-oxidative status (38). One of the pathological factors associated with the onset and progression of asthma is oxidative stress (39). During the process of developing asthma, inflammatory immune cells and epithelial cells produce reactive oxygen species (ROS). The generation of ROS, in higher content than the natural antioxidant capacity of the lungs, leads to oxidative stress and cell damage (40). Excessive oxidative stress has been reported to exacerbate sputum production and inflammation in the airways and damage respiratory epithelial cells (41). Nitric oxide is a free radical and a highly reactive mediator that rapidly reacts with superoxide anions, consequently forming peroxynitrite. Peroxynitrite is a powerful oxidizer that can damage DNA, protein, and fat in biological membranes (42). Previous findings showed that the serum nitric oxide content in a rat receiving *Nasturtium officinale* was slightly decreased compared to the animals in the control group.

Another study evaluated the effectiveness of the herbal medicine called AKLI, which contains the phytochemical component of Picrorrhiza kurroa, and extracts of Zingiber officinale and Ginkgo biloba. Similar results consistent with the present study were also obtained; the efficacy was satisfactory following the asthma quality of life, but no statistically significant changes were found in lung function analyzed by spirometry data (43), which is in line with the findings of the present study. However, other studies also demonstrated the effectiveness of herbal medicines as complementary therapy in asthma (44-46). In the present study, the reason for the lack of improvement in endpoint outcomes may be due to the relatively small sample size. However, while one month was considered long enough to demonstrate an effect on the main study endpoints based on previous studies, a longer intervention period might have been needed to show an effect of *Nasturtium officinale*.

The adverse effects reported for the *Nasturtium officinale* group and the placebo group were all classified as mild. These effects did not result in any withdrawal from the trial. Preclinical toxicology studies in rats have shown that a hydroalcoholic extract of *Nasturtium officinale*, administered sub-chronically in an oral dose of 5000 mg/kg, was safe with no toxicity to the hematopoietic and biochemical systems (47).

The present study has some limitations. One of the major limitations was the limited number of patients with asthma recruited from a single geographical location. Hence, a multicentric study is required to confirm the current study results. Moreover, the efficacy of *Nasturtium officinale* in patients with asthma has to be evaluated over a longer duration of treatment. While the intra-rater intervention was high and consequently reduced error as data extraction was performed by a single researcher, this did not completely rule out the possibility of bias. The present study also has strengths, including the use of a gold-standard RCT-study design with strict inclusion criteria at baseline. Moreover, the questionnaire was based on previously validated instruments.

Conclusion

In conclusion, allowing for the limitations mentioned above, in the current first Randomized Controlled Trial (RCT) study, we were not able to demonstrate any significant effect of the hydroalcoholic extract of *Nasturtium officinale* supplementation on various outcomes. These outcomes include quality of sleep, asthma control, lung function, and quality of life in asthmatic patients. Further adequately powered RCTs are of clinical importance to clarify the potential positive effects of the hydroalcoholic extract of *Nasturtium officinale* on asthma status.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Helsinki declaration and its later amendments. The study was approved by the Ethics Committee of Yasuj University of Medical Sciences, Iran (IR.YUMS.REC.1399.157). Written informed consent was obtained from all patients; all participants were informed that they could withdraw at any point during the trial. This study was prospectively registered at the Iranian Registry of Clinical Trials (www.irct.ir). Trial registration: IRCT20220506054749N1.

Competing interests

The authors declare that they have no conflict of interest.

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Author contributions

RA, EZ, N.SH, ME, HS, AF, FB, and A. HD contributed to the conception, design, and drafting of the manuscript. RA, EZ, and A. HD contributed to data collection. FB, A. HD, and AM contributed to the drafting of the manuscript. All authors approved the final version for submission. A. HD and RA oversaw the study.

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