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Efficacy of the *Punica granatum* peels aqueous extract for symptom management in ulcerative colitis patients. A randomized, placebo-controlled, clinical trial

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A B S T R A C T

Objective: To investigate the effects of the *Punica granatum* peel extract on symptoms of patients with ulcerative colitis (UC).
Method: Patients with UC were randomized to receive an aqueous extract of the *P. granatum* peel (6 g of dry peel/day) or placebo for four weeks complementary to standard medications. Symptoms were assessed using the Lichtiger Colitis Activity Index (LCAI) at baseline, week 4, and week 10 (follow-up). Clinical response was defined by $\geq$ 3 point decrease in LCAI.
Results: The LCAI score was similarly reduced in both the *P. granatum* (-1.68 ± 3.85, $P = 0.019$) and placebo groups (-1.39 ± 2.41, $P = 0.002$). Clinical response was higher with *P. granatum* compared with placebo at week 4 (41.4% vs. 18.2%, $P = 0.055$), but not at week 10 (48.3% vs. 36.4%, $P = 0.441$).
Conclusions: The *P. granatum* peel extract seems effective in complementary management of UC. Further studies in a larger sample of patients are warranted. IRCT2014040617156N1.

1. Introduction

Ulcerative colitis (UC), the most common type of inflammatory bowel diseases (IBD), is characterized by inflammation and ulceration of the mucosal layer of the colon. UC presents with symptoms of rectal bleeding (with or without mucus), diarrhea, tenesmus, and abdominal pain. It has a remitting and relapsing clinical course and requires lifelong treatment [1]. The main current treatments of IBD include administration of topical and/or systemic anti-inflammatory and immune-suppressive agents [1]. In addition to the current standard care, IBD patients often use complementary and alternative medicine (CAM) for the management of their symptoms. Surveys have shown that about half of the patients use various methods of CAM such as probiotics, vitamins, dietary supplements, mind-body medicine, and herbs [2–4]. However, a limited number of well-designed studies are conducted on various CAM methods in IBD patients and a clear conclusion could not be made on the efficacy and safety of most of them [5,6].

Some herbal medicines used by patients and studied in controlled trials include aloe vera, *Triticum aestivum*, *Andrographis paniculata*, curcumin, *Boswellia serrate*, *Plantago ovata*, *Artemisia absinthium*, and *Tripterygium wilfordii* [5]. These herbs have been effective in inducing remission or clinical response when compared with placebo or conventional treatments [5,7]. The mechanisms of action of these herbs in treatment of IBD are not clear. Various biologically active compounds are present in herbal products, some

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of which may have beneficial effects such as antibacterial, antioxidant, and anti-inflammatory actions [8,9].

The pomegranate, *Punica granatum* (Punicaceae), is a fruit cultivated widely in the Mediterranean region. Various parts of the plant have traditionally and medically being used for a variety of complaints such as infections, inflammation, diarrhea, and ulcers. A growing body of recent studies has evaluated potential therapeutic and preventive properties of pomegranate for cancer, cardiovascular diseases, diabetes, dental conditions, and protection from ultraviolet radiation. The main therapeutic ingredients are ellagic acid, flavonoids, and anthocyanins contributing to main therapeutic mechanisms of the herb including anti-oxidant, anti-carcinogenic, and anti-inflammatory properties [10–14].

The potential therapeutic effects of the *P. granatum* extracts for IBD are reported by a number of animal studies. These studies have shown that *P. granatum* extracts attenuates chemical induced colitis mainly attributed to its active ingredient, the ellagic acid [15–18]. To the best of our knowledge, however, there has been no report from a randomized controlled clinical trial on the efficacy of *P. granatum* extracts for IBD patients. Therefore, we aimed to investigate the efficacy of *P. granatum* peel aqueous extract for symptom management in UC patients. We hypothesized that this herbal medicine is effective and safe for improving symptoms in these patients.

2. Materials and methods

2.1. Participant and study setting

This randomized clinical trial was conducted in the gastroenterology clinic of the Integrative Functional Gastroenterology Research Center in Isfahan city (Iran) between January and June 2014. Inclusion criteria were a) age between 18 and 65 years, b) diagnosis of UC by a gastroenterologist based on clinical symptoms, endoscopic appearance, and pathologic studies, c) Lichtiger Colitis Activity Index (LCAI) score of 4–11 indicating moderate disease activity, and d) willingness to participate. Patients with the following characteristics were not included into the trial: a) previous history of allergic response or intolerance to pomegranate compounds, b) opium addiction, c) consuming 15 mg or higher dosage of prednisolone per day, cyclosporine, or anti-TNF agents (e.g. infliximab), and d) pregnant women. Patients with no appropriate treatment compliance and those experiencing disease flare or severe side effects were excluded from the trial. The study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (Tehran, Iran, ethical approval code 400/5790) and informed consent was obtained from patients. The study protocol was registered at the Iranian Registry of Clinical Trials [http://www.irct.ir, registration code: IRCT2014040617156N1].

2.2. Study design

2.2.1. Herbal drug and placebo preparation

The herbal medicine used in this trial was an aqueous extract of the *P. granatum* peel. Preparation of the herbal drug and placebo was done in the Herbal Medicine Laboratory of the Shahid Beheshti School of Pharmacy. The extract was produced from the dry peel of the sweet pomegranate (called 'Anar' in Iran) which has been harvested in Ardakan (Yazd province, Iran). The peels were washed with water, dried, fragmented, and then grinded to produce powder. One liter of warm boiling water (100° degree) was added to 1 Kg of peel powder and kept in closed container in the laboratory for 6 h. The solvent was then filtered and concentrated on water bath to produce 100 mg extract from 1 kg of the dry peel. Herb-to-extract ratio was then 10:1. The *P. granatum* peel extract syrup 10% was produced based on the simple syrup of the United States Pharmacopeia (USP). Finally, each 8 cc of the syrup contained 6 g of the dry peel to be consumed daily. Placebo was prepared based on USP simple syrup formula adding approved additives (Amaranth) to look and smell the same as the *P. granatum* syrup.

2.2.2. Randomization, medication, blinding, and compliance

The study was designed as a randomized, double-blinded, placebo-controlled, clinical trial with two parallel arms. All patients received current standard treatment of UC by the attending gastroenterologists. Patients were equally randomized into two groups of *P. granatum* and placebo. Randomization was done using computer generated random numbers. Patients in the *P. granatum* group consumed 8 cc of the syrup containing 6 g of the dry peel in two divided dose (every 12 h) for four weeks. This dosage of the product and duration of therapy was determined by referring to the PDR for Herbal Medicines [19]. The *P. granatum* and placebo syrup were packed and alphabetically labeled in the same opaque and sealed bottles. Attending physician, patients, principal investigators, and data analyzer were blinded to the study arms. A co-investigator who was not involved in patients' recruitment or allocation or in outcome assessment was aware of the drug codes and cleared it after data analysis. After enrollment, a co-investigator assigned patients to their groups. Patients' compliance was checked every week by live interview or telephone call.

2.3. Measurements

Symptoms of UC were assessed using the LCAI which is frequently being used by clinical trials on UC and include both objective (e.g. number of stools) and subjective (e.g. degree of pain) items [20]. It contains eight items which evaluate a. diarrhea graded from 0 (0–2 daily stool frequency) to 4 (10 or more daily stool frequency), b. nocturnal diarrhea (yes/no), c. rectal bleeding graded from 0 (<50% of movements) to 3 (100% of movements), d. fecal incontinence (yes/no), e. abdominal pain/cramping graded from 0 (none) to 3 (severe), f. general well-being graded from 0 (perfect) to 5 (terrible), g. abdominal tenderness graded from 0 (none) to 3 (severe or rebound), and h. need for anti-diarrhea medications (yes/no). The total score is ranged from 0 to 21 [20]. Based on available data on comparison of the LCAI with biological and endoscopic markers of disease activity in UC patients [21], we concluded that LCAI scores of 4–11 indicates a partially active disease state, i.e. not so inactive that need no complementary medication, neither so active that needs a major therapeutic intervention; otherwise our study might face an ethical dilemma or a logical one. The LCAI was completed by patients (or by interview if needed) after explanation by the principal investigators. Assessment was done at baseline, at week 4 (end of medication), and then at week 10 (drug free follow-up). Side effects were assessed by interviewing with patients.

2.4. Data analyses

2.4.1. Primary and secondary outcomes

The primary outcome of the study was the changes in LCAI score after treatment. Clinical response was defined by a decrease in LCAI of greater than or equal to 3 points [22]. Secondary outcomes were considered as change in each of the symptoms included in the LCAI and the treatment side effects.

2.4.2. Sample size calculation

Sample size was determined considering type I and II error rates of 5% and 20%, respectively. Minimum detectable effect size (i.e. Δ of clinical response) was considered to be of 30% based on a similar