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Original article

# The effect of *Elaeagnus angustifolia* L. whole fruit and medulla powder on women with osteoarthritis of the knee: A randomized controlled clinical trial

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**Abstract**

*Introduction:* In this clinical trial, the effect of *Elaeagnus angustifolia* L. whole fruit and medulla powders on clinical symptoms of females with knee osteoarthritis (OA) was investigated.

*Method:* In the present randomized double blinded placebo-controlled study, ninety females with mild to moderate knee osteoarthritis were randomly assigned to one of three groups – medulla powder, whole fruit powder or placebo for 8 weeks. The WOMAC index was used as a primary outcome and crepitus, swelling, and joint instability were assessed as secondary outcomes before and at the end of supplementation.

*Results:* After 8 weeks of supplementation, compared with the baseline, significant reductions in scores of pain, stiffness and physical function were observed in the two supplemented groups, however, the reduction of these values was not statistically significant in the placebo group. There were significant differences between the patients receiving medulla powder and the placebo group in the case of changes in pain ($p < 0.001$) and physical function ($p = 0.001$) scores. However, no significant differences were found between the whole fruit powder and the placebo groups or between the two supplemented groups for changes in any scores ($p > 0.01$). The number needed to treat (99%CI) values for patients who consumed medulla and whole fruit powders for at least 50% improvement in pain, were 3 (2–40) and 6 (−9 to 2), respectively.

*Discussion:* Generally, medulla powder of *E. Angustifolia* L. had positive effects, especially in improving pain as well as stiffness and physical function in females with knee OA.



*Keywords:* *Elaeagnus angustifolia* L.; Females; Osteoarthritis; Clinical symptoms

## Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder that can develop in any joint in the body, but the knees are one of the most commonly affected joints since they are the primary weight-bearing joints of the body [1,2]. The prevalence of osteoarthritis is about twice as high in women as men [3]. Gender differences have been noted for OA at epidemiologic, radiographic, circulating biomarker, hormonal, and cellular levels [4]. Osteoarthritis is a major cause of morbidity, disability, loss of function, and impaired quality of life, mostly in the aging population [1]. Due to an increasingly aging population, OA represents a substantial burden on healthcare in both developed and developing countries [1].

The main symptoms of OA include pain, morning stiffness, joint swelling, crepitus and limited range of motion, restriction of social activities and/or compromised work capacity [5]. There is no cure for OA and the aim of available treatments is reducing symptoms such as pain and inflammation, maintaining joint mobility, and limiting the loss of function [6]. The most frequently used agents in the treatment of OA are glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs). However, these drugs do not provide a complete improvement and are

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associated with side-effects [7]. The main side-effects of these drugs are systemic toxicity that can affect the gastrointestinal, cardiovascular, and renal systems [8–10]. As a result, non pharmacological complementary treatments have become more common. The College of Rheumatology (ACR) or the Osteoarthritis Research Society International (OARSI) recommends both non-pharmacological and pharmacological approaches for the management of knee OA [11,12]. The non-pharmacological interventions mostly include education and self-management, physical therapy, aerobic, muscle strengthening and water-based exercises, weight reduction, walking aids, knee braces, footwear and insoles, thermal modalities, transcutaneous electrical nerve stimulation and acupuncture, and herbal and botanical agents [12]. There are many botanical and herbal agents which have been assessed for their effects on osteoarthritis, such as green tea [13], ginger [14], avocado, soybean extract [15].

One herbal agent that is commonly utilized in Iran is *Elaeagnus angustifolia* L., which, in traditional medicine, is widely used in treatment of urinary diseases, gastric disorders, diarrhea, nausea, vomiting, jaundice, asthma, and flatulence [16,17]. *E. angustifolia* L. fruit is one of the most commonly used Iranian folk medicine for treating pain, especially in rheumatoid arthritis [18]. Studies have shown the anti-nociceptive, anti-inflammatory, and muscle relaxant effects of this fruit in animal models [19,20]. In Iran, this fruit is consumed in two forms; whole fruit powder (i.e., the grounded whole fruit powder including seed, medulla, and pericarp) and simply the pulp of the fruit by itself, which is available in local markets or Iranian traditional medicinal plants stores.

Owing to an aging population and consequently, increasing prevalence of osteoarthritis, especially in women, and also because of the adverse effects of the commonly used drugs, there is an increasing need to investigate the potential of herbal remedies to use as a complementary treatment in addition to routine therapies for improving symptoms in these patients. Despite the frequent use of *E. angustifolia* L. as a complementary medicine in arthritis, to the best of our knowledge, there is a lack of human data in this regard. The present study was designed to evaluate the effect of whole fruit and medulla of *E. angustifolia* L. powder supplementation on symptoms of female patients with knee osteoarthritis.

## Method

### *Subject selection*

One hundred and twenty patients with knee osteoarthritis with disease severity from mild to moderate based on the criteria of the American College of Rheumatology (ACR) [21] and referred to the Rheumatology Centre of Sina Hospital-Tabriz-Iran, were selected for the study.

The patients were included if they were female, aged 40–70 years, had moderate to severe bilateral primary knee osteoarthritis (according to ACR classification) and body mass index (BMI) of 25–34.9 kg/m$^2$. The patients were excluded if they had secondary osteoarthritis, active synovitis, neurological disorder that affects movement, muscle control and balance, uncontrolled hypertension, diabetes, cardiovascular disorders, chronic kidney disorders and functional liver disorders, were using Frosemid, Probenecid, Anticoagulants, Hydantoin, Sulfonamides, Methotrexate, Lithium salts, Beta blockers and muscle relaxants, smoked, or had an allergic reaction to *E. angustifolia* L., and were using *E. angustifolia* L. regularly.

The sample size was designed to detect 50% reduction in pain intensity of knee with 90% power and a type I error rate of 1%, which necessitated at least 25 cases in each group. The volunteer patients were randomly assigned to the two treatment groups or placebo group using a computer-generated random number table. Randomization was performed with the use of sealed envelopes. The investigator and participants were blinded to group allocation. The randomization code was only revealed after the statistical analyses were completed.

Ethics approval was received from the ethic committee of Tabriz University of Medical Sciences (reference number 91171), and the study was registered with the Iranian Registry of Clinical Trials (http://www.irct.ir) and given the identification no. 201208241197N13. All patients were made aware of the content of the study and informed written consent was obtained from all participants.

### Study design

The present study was a double blind randomized placebo-controlled trial in which the patients were randomly assigned to two interventions or a placebo group. The patients in the first and second intervention groups ($n = 30$ for each group) were supplemented with 15 g/day whole fruit powder and medulla powder of *E. angustifolia* L. and the patients in placebo group received 15 g/day corn starch with Isomaltose for 8 weeks. All supplements were identically packaged to be indistinguishable. Patients were recommended to consume one packet daily for 8 weeks, preferably with milk after meals to reduce gastrointestinal complications.

All patients underwent routine physical examinations and conventional treatments such as Acetaminophen (*Tylenol*) and Non-Steroidal Anti-inflammatory Drugs (Celecoxib, Ibuprofen, Naproxen) continued during the course of the study. The use of conventional drugs and treatments was recorded at baseline, at week four, and at the end of week eight. BMI (weight (kg)/height (m$^2$)) was calculated from height and weight which were measured using standardized protocols and calibrated equipments. The Persian version of WOMAC index (i.e., Likert version) was used as a main outcome measure, which was completed through face-to-face interviewing [22]. This questionnaire was shown to be a reliable and valid instrument for evaluating the severity of knee OA in Iranian patients [22]. The WOMAC index is usually used to assess patients with osteoarthritis of the hip or knee using 24 parameters in three sections of pain (five questions), stiffness (two questions) and physical functions (17 questions). It can also be used to monitor the course of the disease or to determine the effectiveness of anti-rheumatic medications.

The changes in the status of swelling, crepitus and join instability, which were measured by a Likert index, were also used as a secondary outcome. The questionnaire had acceptable