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Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Effect of a traditional syrup from *Citrus medica* L. fruit juice on migraine headache: A randomized double blind placebo controlled clinical trial

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ARTICLE INFO

Article history:

Received 27 June 2015

Received in revised form

13 November 2015

Accepted 21 December 2015

Available online 22 December 2015

Keywords:

Citron

Citrus medica

Migraine headache

Juice syrup

Persian Traditional Medicine

Clinical trial

ABSTRACT

Ethnopharmacological relevance: In Persian ethnomedicine several herbal remedies and functional foods have been used to treat migraine headache which are mostly summarized in *Qarabadin-e-kabir* (Aghili-Shirazi MH, 1773). One of them is Citron syrup (Sharbat-e-Balang) containing edible *Citrus medica* L. fruit juice and sugar. The present study was designed to assess the efficacy and safety of Citron syrup on patients with migraine headache.

Materials and methods: Citron syrup was prepared as described in *Qarabadin-e-kabir*. In this double blind randomized placebo-controlled clinical trial, ninety patients with migraine headache were allocated to three parallel groups (Citron syrup, propranolol or placebo). Patients received 15 ml of Citron syrup, placebo syrup or 20 mg of propranolol tablet three times daily after a meal for 4 weeks. Primary outcomes were obtained from three measures: the frequency (per month), mean duration (hour) and mean intensity (visual analogue scale "VAS" 0–10 score) of headache attacks evaluated prior to and following 4 weeks of the intervention.

Results: Citron syrup was superior to placebo in reduction of headache attacks intensity ($P < 0.01$) and duration ($p < 0.0001$) and as effective as propranolol in patients with migraine headache ($P > 0.05$). However, unlike propranolol, Citron syrup could not significantly reduce the frequency of attacks compared to placebo. No indication of any serious side effects from Citron syrup was observed.

Conclusion: According to obtained results, Citron syrup as a traditional Persian remedy can be suggested as an effective treatment for decreasing pain intensity and duration of attacks in migraine headache and the effectiveness is comparable to propranolol. However, the syrup did not show significant effect on frequency of attacks.

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1. Introduction

Headache is a very common disorder with lifetime prevalence of about 96% in general population. The point prevalence of headache is 11% in men and 22% in women (Rasmussen et al.,

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1991). Migraine is among the most common types of headache which affects up to 12% of the general population (Lipton et al., 2001). It is more frequent in women with 1-year prevalence of 15–18% of women and 6% of men (Mathers et al., 2003). Multiple therapeutic modalities are recommended in patients with migraine headache including pharmacologic and non-pharmacologic treatments for prevention and treatment of migraine attacks. Pharmacologic preventive treatments include beta blockers, antidepressants and anticonvulsants though there is insufficient response to these drugs. Scientific evidences show that only two thirds of the patients who received these treatments will have a 50% reduction in the frequency of headaches. On the other hand,

the required doses for the mentioned response may cause intolerable side effects (Goadsby et al., 2002).

A wide range of complementary and alternative options are evaluated in management of migraine because of inadequate therapeutic response to current conventional treatments (Mauskop, 2012). Herbal therapies as the most popular type of complementary and alternative medicine are used and evaluated in patients with migraine (D'Andrea et al., 2014).

Traditional Persian medicine (TPM) has an extended and rich history in diagnosis and treatment of different headache types (Zarshenas et al., 2013). Avicenna, Aghili Shirazi and other medieval Persian physicians dedicated the important part of their manuscripts to headache disease and therapies. Herbal medicines were the most common natural remedies prescribed by Persian physicians for headache treatment (Aghili, 1771). Reviewing the literature of TPM shows that *Citrus medica* L. fruit has been a good candidate recommended to the patients with headache (Aghili, 1771; Ibn-nafis, 2008; Mall, 2010). The fruit of *C. medica* L. commonly known as Citron or Persian apple belongs to the genus Citrus and is a member of Rutaceae family (Mozaffarian, 2004). In the medieval Persia literatures, different names were commonly used for Citron including *balang*, *otranj*, *toranj*, *badrang*, *vadrang*, *bazrang*, *torang* and *mottak* (Biruni, 2004). The plant has a global distribution in the Asia, the Mediterranean and central and southern parts of America (Zargari, 2012). It appears that a few centuries ago, the traders brought the fruit from the eastern Asian countries to Persia and then it was distributed and cultivated in north and south parts of Persian land (Ensminger and Ensminger, 1993; Zargari, 2012).

Medieval physicians have recorded a broad spectrum of medicinal uses for various parts of Citron tree. Citron yellow peel is believed to show tonic effect for main organs like heart, stomach, liver and brain. Citron peel oil has been externally used for paralysis, osteoarthritis and sciatica. The fruit seeds in the traditional dental formulations could strengthen the gums. The leaves of Citron are known to have anti-flatulence effects and have been consumed as the stomach tonic and visceral stimulant. Citron juice boiled with sugar has been used as a headache remedy (Aghili, 1771; Arias and Ramón-Laca, 2005). *Qarabadin-e-kabir* (Aghili-Shirazi, 1773), as one of the most important ancient pharmaceutical manuscripts introduced several formulations containing different parts of Citron tree for treatment of wide range of diseases including headache. One of these formulations is Citron syrup called “Sharbat-e-Balang”. In Persian ethnomedicine Sharbat-e-Balang (Citron syrup) has been known as a tonic for stomach which can relieve headaches triggered by gastrointestinal complaints (Aghili, 1771; Avicenna (IbnSina), 2005; Ibn-nafis, 2008).

Some pharmacological studies have been carried out to investigate the biological properties of different parts of Citron plant in order to validate its traditional medical uses. There are some evidences indicating that Citron whole fruit possess analgesic properties (Negi et al., 2010), antioxidant (Al-Yahya et al., 2013) and insulin secretagogue and slimming effects (Peng et al., 2009). Menichini et al. (2011a) also showed that the immature Citron fruits had a remarkable antioxidant properties and inhibited α -glucosidase activity. In vivo studies have shown the antiulcer activity of the Citron fruit aqueous extract (DS et al., 2011; Nagaraju et al., 2012). The Citron fruit juice antimutagenicity, anticancer effects (Entezari et al., 2009) and antimicrobial properties (Shende et al., 2015) were also reported previously. The in vitro studies carried out in the presence of Citron juice, showed the inhibitory effect on the growth of Struvite crystals. The pharmacological investigations indicated that Citron leaves extract had the antioxidant activity and inhibitory effect on the Nitric oxide production. In vitro assessments also showed that Citron leaves extract could ameliorate hyperglycaemia by affecting glucose

homeostasis related enzymes (Menichini et al., 2011a). In addition, other studies reported anthelmintic (Bairagi et al., 2011) and estrogenic activities for leaves (El-Alfy et al., 2012; Sharangouda, 2007). The seeds extracts possessed the antidiabetic and hypolipidemic activity (Sah et al., 2011). A number of investigations indicated that Citron peels was able to reduce plasma glucose concentration and lowered the levels of plasma cholesterol and triglycerides (Menichini et al., 2011b). The antimicrobial and anthelmintic properties of Citron peels were also reported (Kabra et al., 2012; Kabra et al., 2011). Although some investigations showed that citrus fruits may be trigger for migraine headache, it was found no evidence for Citron fruit in literatures (Eagle, 2012; Millichap and Yee, 2003). Although several studies have been performed on the pharmacological activities of this fruit but the exact mechanism of action of Citron syrup in controlling headache is not well known. In Some in vitro studies the anti-inflammatory and analgesic activities of the whole fruit have been reported (Negi et al., 2010). The presence of nutraceutical and potential compounds like organic acids, polyphenols and flavonoids in Citron fruit juice possibly have important role in its effectiveness. Several investigations suggested that some antinociceptive actions could be attributed to flavonoids, polysaccharides and organic acids (Abdel-Salam and Baiuomy, 2008; Kakeda et al., 2008). So, high content of organic acid and carbohydrates in Citron syrup possibly has an effective role in mechanism of action. The potential compounds like bioflavonoid and polyphenols have the main effects on the inflammatory pathways and nitric oxide activity (Garg et al., 2001; Kozłowska et al., 2010; Loscalzo et al., 2011; Menichini et al., 2011a). Furthermore, according to the some evidences about the oxidative stress in pathogenesis of migraine, the antioxidant components of this fruit may be of importance (Alp et al., 2010).

Moreover, to our knowledge, no clinical trial has been approved to investigate the effect of Citron on migraine headache. According to its ethnopharmacological application in TPM, this study was designed to evaluate the efficacy and safety of Citron syrup in patients with migraine headache in a randomized clinical trial.

2. Materials and methods

2.1. Drug and placebo preparation

The fresh fruits of Citron were collected in December 2013 from Jahrome, a city located in east of Fars province, Iran and authenticated by a botanist (S. Khademian). Voucher specimens of *C. medica* L. (No. 749) were deposited in the Herbarium of Department of Traditional Pharmacy, Shiraz School of Pharmacy. The peels were removed thoroughly and then Citron juice was extracted by a fruit juice extractor. The collected juice was passed through a strainer (mesh 100) to remove pulp and seeds.

The formulation of Citron syrup was prepared according to methods described in the traditional Persian pharmacopeia like *Qarabadin-e-kabir* (Aghili-Shirazi, 1773) and *Qarabadin-e-salehi* (Heravi, 1765). Briefly the equivalent weight of sugar was added to clear Citron juice and the mixture was heated at 80° for one hour to decrease the syrup volume to 60%. The prepared syrup had a viscose texture with a brownish colour.

Placebo formulation was simple syrup which contained NaCMC 1%, citric acid 1.5%, sodium benzoate 0.2% and FD&C colour brown qs. Propranolol tablet 20 mg three times a day was considered as the standard treatment in this trial.

2.2. Clinical study

The study was designed as a parallel randomized controlled clinical trial using three arms with a 1:1:1 allocation ratio

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