Journal of Ethnopharmacology 172 (2015) 325–332

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

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

The efficacy of whey associated with dodder seed extract on moderate-to-severe atopic dermatitis in adults: A randomized, double-blind, placebo-controlled clinical trial

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ARTICLE INFO

Article history:
Received 14 December 2014
Received in revised form
29 June 2015
Accepted 3 July 2015
Available online 4 July 2015

Keywords:
Eczema
Flavonoids
Traditional medicine
Atopic dermatitis
Whey associated with dodder seed extract

Chemical compounds studied in this article:
Quercetin (PubChem CID: 5280343)
Kaempferol (PubChem CID: 5280863)
Rutin (PubChem CID: 5280805)

ABSTRACT

Ethnopharmacological relevance: Atopic dermatitis is a common chronic inflammatory skin condition that is on the rise and adversely affects quality of life of the affected individual. Dry skin and pruritus, major characteristics of this disease, are associated with the dysfunction of the skin barrier. Though mild cases of the disease can be controlled with antihistamines and topical corticosteroids, moderate-to-severe cases often require treatment with immunomodulatory drugs, which have many side effects. It is now more common to use complementary and alternative medicines in the treatment of atopic dermatitis. In traditional Iranian medicine, the use of whey with the aqueous extract of field dodder (*Cuscuta campestris* Yunck.) seeds in severe and refractory cases of atopic dermatitis is common and has no side effects.

The aim of this study was to assess the efficacy and safety of whey associated with dodder seed extract in the treatment of moderate-to-severe atopic dermatitis in adults.

Materials and methods: The study was a randomized, double-blind placebo control trial that was conducted on 52 patients with moderate-to-severe atopic dermatitis for 30 days. In this study patients received freeze dried whey powder with spray dried water extract of field dodder or the placebo for 15 days. At baseline (week zero), after the end of the 15 day treatment period (week three) and 15 days after stopping the drug or placebo (follow-up/week five), patients were evaluated in terms of skin moisture, elasticity, pigmentation, surface pH and sebum content on the forearm with Multi Skin Test Center® MC1000 (Courage & Khazaka, Germany) and the degree of pruritus and sleep disturbance in patients were also recorded.

Results: 42 patients completed 30 days of treatment with the medicine and the follow-up period. At the end of the follow-up period a significant increase in skin moisture and elasticity in the group receiving whey with dodder was observed compared with the placebo group ($p < 0.001$). There was a significant difference between the two groups regarding the pruritus after 15 days of receiving treatment or the placebo ($p < 0.05$), and at the end of the 30-day study period the difference was clearly significant ($p < 0.001$). Sleep disturbance showed significant changes at the end of follow-up period ($p < 0.05$). There was no significant difference between the two groups concerning changes in skin pigmentation, however, a significant decrease was observed in the group receiving whey associated with dodder seed extract over time ($p < 0.001$). There were no significant alterations in skin surface pH and the amount of sebum between the two groups. Temporary side effects were reported including anorexia and mild gastrointestinal problems in drug use.

It is noteworthy that in this study despite the fact that patients received whey with dodder for just 15 days, moisture and elasticity of the skin continued to increase in the second half of the study (follow-up period). This shows that the effect of whey with dodder is not transient and this drug really helped skin barrier reconstruction and accelerated the healing process of skin. This positively influenced the skin parameters and consequently the improvement of pruritus and sleep disturbance.

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http://dx.doi.org/10.1016/j.jep.2015.07.003

Conclusions: The results indicate that whey associated with dodder seed extract can serve as a promising alternative for the treatment of moderate-to-severe atopic dermatitis.
Trial registration: Iranian Registry of Clinical Trials IRCT2013121415790N1.

1. Introduction

Atopic dermatitis (AD) is a common chronic inflammatory and pruritic skin disease, often associated with a positive family history of allergic diseases, such as allergic rhinitis and asthma (Leung et al., 2004). The disease has a devastating effect on quality of life. The eczematous skin lesions with severe pruritus lead to disrupted sleep and decreased daily performance and social activities of patients in addition to significant financial expenses for both the families of patients and society, as well (Fivenson et al., 2002). AD affects 15–30% of children and 2–10% of adults (Bieber, 2008). Prevalence in developing countries is more than 10% in the general population and is increasing day by day, while in developed countries prevalence has reached a level plateau of approximately 20% (Kim, 2013). Atopic dermatitis occurs in those who are genetically predisposed. Mutations in the filaggrin gene, which is a key protein in formation of the skin barrier and skin moistening, lead to skin barrier dysfunction. Skin barrier damage increases transepidermal water loss and permits the entry of environmental antigens and allergens from the epidermis leading to inflammatory responses (Howell et al., 2009). Topical corticosteroids, emollients and oral antihistamines are used in mild disease without too many side effects, but many patients with moderate-to-severe atopic dermatitis require systemic immunomodulating treatment (e.g., cyclosporine, azathioprine, systemic corticosteroids and methotrexate) with unfavourable side effects (Hong et al., 2011; Roekevisch et al., 2014).

Since effective treatments for the disease are limited, there is a tendency toward finding better and safer therapies. Among them, the use of complementary and alternative medicines (CAM) is growing in the treatment of inflammatory skin diseases, particularly AD (Boneberger et al., 2010). Traditional Iranian Medicine (TIM), with a long history of several thousand years, offers effective treatments in this field with diet and lifestyle modification and drugs of a plant or animalistic origin. TIM recommends the use of topical emollients and wet compression in mild AD. In TIM, one of the most common treatments for chronic and severe cases of atopic dermatitis is the use of whey with the aqueous extract of field dodder seeds (Avicenna, 2005; Rhazes, 1990).

Whey is a protein complex derived from milk and considered a functional food. Whey has several properties as an antitumor, antihypertensive, hypolipidaemic, antiviral, antibacterial, anti-ageing and chelating agent. Whey possesses potent antioxidant activity as a result of intracellular conversion of the amino acid cysteine into glutathione, which is an intracellular potent antioxidant (Marshall, 2004). Whey's healing properties have been recognized since the 5th century BC and whey cure has been recommended by Hippocrates, Galen, Avicenna, Rhazes, and other famous names from the history of medicine. Whey has been used for medicinal purposes, including gout, sepsis, wound healing, as well as liver and stomach diseases (Avicenna, 2005; Rhazes, 1990; Smithers, 2008; Vasey, 2006).

Field dodder, with the scientific name of *Cuscuta campestris* Yuncker (Family Convolvulaceae) and traditional name of aftimoun, is a parasitic plant without leaves, yellowish green stems climbing the winder and sweet-scented white flowers (Fernald, 1970). Different *Cuscuta* species are widely used as medicinal plants in traditional medicine in the treatment of epilepsy, psychosis, paralysis, cancer, skin diseases, etc. (Aghili Khorasani, 2011a). *C. campestris* Yunck. is the most widespread species in the genus *Cuscuta* in the world (Holm et al., 1997). This plant has analgesic, hypothermic, anti-inflammatory, anti-proliferative effects and CNS depression activity (Agha et al., 1996). *Cuscuta* seed extract contains a variety of flavonoids, polysaccharides, alkaloids and other chemicals. Among the flavonoids, quercetin is a therapeutic compound for inflammatory and autoimmune diseases with immunomodulating effects (Lee et al., 2011).

The aim of this study was to assess the efficacy and safety of whey associated with dodder seed extract (WaDSE) in the treatment of moderate-to-severe atopic dermatitis in adults that was conducted as a randomized, double-blind, placebo-controlled trial.

2. Materials and methods

2.1. Patients

52 patients with moderate-to-severe atopic dermatitis referred to the Dermatology Clinic of Afzalipour Hospital, Kerman University of Medical Sciences, Iran, have entered into the trial after the confirmation of diagnostic criteria for atopic dermatitis (Hanifin and Rajka, 1980). Inclusion criteria were as follows:

- Hanifin and Rajka criteria approved for atopic dermatitis.
- Moderate-to-severe atopic dermatitis (SCORAD $\geq$ 25).
- Aged 18 and older.
- Poor response to conventional treatment for atopic dermatitis (topical steroids and antihistamines).
- AD consistently symptomatic for at least six months.
- Lack of exudates or infection.
- Lack of pregnancy and lactation.
- The absence of concomitant systemic disease (except asthma and allergic rhinitis).

Patients with abnormalities in blood cell count, liver enzymes and renal function tests, secondary bacterial infections, who were receiving systemic corticosteroids and other immunosuppressant drugs and phototherapy during the study or who demonstrated drug intolerance symptoms were excluded.

Prior to intervention, informed written consent was obtained from all patients and patients in both groups were asked to continue previously received topical steroids with the same strength and frequency. This study was approved by the Medical Research Ethics Committee, Shahid Beheshti University of Medical Sciences.

2.2. Drug and placebo preparation

In traditional medicine, field dodder seed is used in the treatment of chronic atopic dermatitis as a decoction associated with whey. In this study, dosage form change was necessary for uniformity and ease of use. Thus, a powder form of whey was prepared, and as the dodder seed decoction has a bitter taste, dried aqueous extract was prepared and administered in capsule form.

2.2.1. Whey

In traditional medicine, whey is produced using three methods: