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**A Comparison of the Efficacy of *Plantago major* Aqueous Extract with Cetirizine in Treatment of Acute Urticaria: a Double-blind, Randomized Controlled Trial**

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**ABSTRACT**

Urticaria, as one of the skin disorders affecting patients' quality of life is characterized with pruritic erythematous and edematous self-limited lesions. Regarding the hypersensitivity nature of this disorder, suppression of mast cell activity and antihistamine release constitutes the core of current therapeutic guidelines. In Persian traditional medicine *Plantago major* L. (*Plantago*) has been frequently mentioned effective in treatment of urticarial lesions. The aim of this study was to evaluate the effects of *Plantago* on urticarial lesions and compare it with the common antihistamine, Cetirizine. In this double-blind randomized clinical trial, 48 patients with urticaria, referred to dermatology wards of Razi, Loghman, and Tajrish clinics, Tehran, Iran, were followed up during the year 2013. Participants were randomly divided into two groups, each being treated with either *Plantago* extract or cetirizine. The number of lesions was recorded daily and satisfaction was evaluated depend on type of treatment. Data were analyzed with SPSS software (version 17.0). A total of 48 patients including 20 males and 28 females with the age range of 10 to 70 were participated in this study. The median duration of therapy was 4.086 and 6.545 days for *Plantago* and Cetirizine, respectively. Based on results, *Plantago* proved to be more effective, although the difference was not statistically significant. The results of this study indicated that *Plantago* extract would be applied in treatment of patients with urticaria, as there was a near-significant decrease in duration of treatment.

**Key words:** Urticaria; *Plantago major* L ; Cetirizine; Traditional Medicine; Patient Satisfaction

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## INTRODUCTION

Urticaria is one of the most common skin disorders that can markedly affect on patients' quality of life that is associated with multi strategy management in almost every case [1]. The common symptoms related to urticarial include: transient pruritic, erythematous and edematous lesions of the skin that gradually disappear within a few hours[2]; hence, diagnosis is usually based on patients' history and clinical features of the disease [3]. Although several studies have been conducted to elucidate physiopathology of urticaria, the exact cause remains unknown. However, a variety of mechanisms have been suggested as the predisposing factors, which may be contributory to emergence and exacerbation of urticaria [4]. Regarding that histopathological reactions including dilatation and hyper-permeability of local capillaries, ultimately leading to angioedema, are cardinal signs of urticaria, it seems that activation of mast cells and histamine release play important role in the progression of this disease [5]. Nevertheless, researches to find the underlying principles of mast cells degradation have remained inconclusive. It should also be noted that not all types of urticaria are responsive to antihistamines, which are currently the first line of treatment [6]. Based on the hypersensitivity phenomena involved in urticaria, various therapeutic methods are used to suppress the activity of mast cells and decrease the release of histamines[7]. Despite the effectiveness of glucocorticoids and immunosuppressive agents such as Cyclosporine in reducing the inflammatory signs, prolonged use of these drugs may bring about severe side effects [8,9,10]. Cromoglycates, as another group of drugs that can stabilize mast cell membrane, are not able to effectively subdue the release of antihistamines in the skin because of low systemic absorption [11,12]. Thus, the current guidelines are focused on the use of antihistamines [13]. While the first generation of antihistamines can easily cross blood-brain barrier and cause remarkable sedation, the decreased lipophilicity of the second generation has significantly minimized CNS side effects[14]. Following the resistance to antihistamines in the treatment of urticaria and also restricted usage in renal and hepatic impairment, patients' satisfaction in usage of antihistamines is decreasing[8,15,16]. Several references in Persian traditional medicine point out to urticaria and related herbal treatments. Lack of clinical trials, investigating the accuracy of these manuscripts, impelled us to design this study with the purpose of evaluating the anticipated efficacy and complications of these methods. Thus, the aim of this subject was to compare the therapeutic effects of Plantago , a common herbal remedy, with Cetirizine, the medication of choice among second generation of antihistamines.

## MATERIALS AND METHODS

In this double-blind randomized clinical trial, 48 patients with urticaria, referred to dermatology wards of Razi, Loghman, and Tajrish clinics, were followed up during the year 2013. Exclusion criteria were included: mean age lower than 10 or higher than 70 years old, history of autoimmune or immunodeficiency disorders, consumption of antihistamines or corticosteroids in the previous month, pregnancy and any recorded hypersensitivity to drugs used in this study. Patients were randomly divided into two groups. The first group received 10% Plantago major aqueous extract, which was prepared using simple USP syrup with 63% glucose after boiling 10 gr seeds in water; while the second group was treated with cetirizine syrup. Patients of both groups were instructed to take their medications two times per day (10 cc per day) and to count the number of urticarial lesions which they had experienced during the day each evening. Improvement of patients' condition were investigated regarding the amount of itching, drug resistance, and side effects on the days 3 and 15 by visiting a dermatologist at the clinic and also on the 6<sup>th</sup> and 9<sup>th</sup> days thorough phone calls. At the end of the follow ups, patients were asked about their satisfaction of treatment. SPSS software (version 17.0) and independent sample t-test were used for statistical calculations and comparison of the groups.  $P \leq 0.05$  was considered as statistically significant. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. Informed consents were obtained from all the study participants at the initial visit and before administration of the drugs.

## RESULTS AND DISCUSSION

A total of 48 patients including 20 male and 28 female with the age range of 10 to 70 participated in this study. Patients' response to therapy occurred on the days 1, 2, 7 and 14 following the administration of drugs. Both groups contained patients who had resistant urticaria with no recuperation during the course of therapy (Table1). In cases where treatment with Plantago aqueous extract continued more than one day, lesions increased at first; for example, patients who were significantly improved on the 7<sup>th</sup> day had the highest number of lesions on the 3<sup>rd</sup> day. However, in the patients of cetirizine group the number of lesions was stable till the 3<sup>rd</sup> day and then started to diminish up to

the 7<sup>th</sup> day. The results showed a noticeable improvement in the number of lesions in patients treated with Plantago (Mean: 4.0886) compared to the group that received Cetirizine (Mean: 6.5454) (P value< 0.07).

**Table 1 - Duration of patients' response and improvement of urticarial lesions after administration of Plantago major and Cetirizine .**

Response Duration	Plantago major aqueous extract	Cetirizine
1	6	5
2	9	3
7	6	9
14	2	5
Resistant to therapy	1	2

Plantago major, also known as plantain, is an herbal species belonging to the family Plantaginaceae, which grows in temperate zones worldwide. The use of plantago leaves dates back to the 1<sup>st</sup> century A.D. as used by traditional Greek physicians in order to wound healing. A broad range of therapeutic features including anti-inflammatory, antimicrobial, antiviral and antitumor effects have been attributed to the plant constituents, such as phenols, terpenoids and iridoids [17,18,19]. As well as its well-known utilization of leaves, either whole or crushed, even the juice of seeds are widely used [20,21]. The biochemical functions of this herb have been investigated in some recent researches. A possible role for cyclooxygenase (COX) 2 inhibitors has been suggested in the treatment of chronic urticaria [22]. Furthermore, an in vitro study by Ringbom *et al.* has shown, ursolic acid, a triterpenoid from plantago, can directly inhibit COX-2 catalyzed prostaglandin production [23]. Another chemical compound, Luteolin a flavonoid in plantago, has been shown to suppress migration and activation of leukocytes, degranulation of mast cells and interleukin-5 bioavailability, which are all regarded as potential strategies in the treatment of urticaria [24,25]. Alcoholic extracts of plantago leaves (with concentrations of 0.5 mg/ml) can deploy high inhibitory activity (more than 80%) on IgE-dependent histamine release from RBL-2H3 cells, a tumor analog of mast cells. Results of this study indicated that active compounds of the extract inhibit mast-cell degranulation, and provide insight into the development of novel drugs for treating allergic skin manifestations [26]. Besides the anti-inflammatory properties, which may be due to COX-2 inhibitory effect, plantago has also been reported as a hepatoprotective and antioxidant agent, which makes its use much more prudent in comparison to antihistamines [27,28]. Investigation of histopathologic changes of lung in asthmatic male rats has proved that hydroalcoholic extract of plantago can decrease the number of mast cells [29]. Baicalein, a flavonoid and a free radical scavenger, is known for its special ability to inhibit cytokines induced by mast cells. Also, Aucubin, as the major irioid glycoside isolated from plantago leaves, can specifically halt the activation of nuclear factor-kappa B (NF-κB) in mast cells and thus lessen the urticarial signs [30]. Our results demonstrated that use of aqueous extract of plantago can exhibit conspicuous effects in the treatment of urticaria and considering the limitations of antihistamine use it is recommended as another choice of therapy.

### CONCLUSION

In this study, we sought to assess the efficacy of plantago on treatment of urticarial lesions and make a comparison with cetirizine. The duration of therapy was noticeably shorter in patients treated with Plantago major extract than in patients of cetirizine group although there was not significant statistically. It is suggested that plantago can be safely used as an alternative remedy in urticaria.

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