

## Feature Article

# Evidence-Based Therapies of Chinese Medicine for Chronic Urticaria: Where Do We Stand and Where Are We Going?

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**ABSTRACT** Chronic urticaria (CU) is characterized by repeated occurrence of wheals or itching for more than 6 weeks. When urticaria symptoms repeatedly occur despite taking Western medicines such as antihistamines, Chinese medicine (CM) has been shown to relieve symptoms and prevent recurrence. However, the lack of robust evidence from the evidence-based medicine perspective is hindering acceptance of CM by the Western medicine community. In recent years, more and more evidence-based studies of CU treatment by CM were report in English literatures, including acupuncture, herbs, and food, although some of evidence is still with low quality. These progress in CM treatment of CU will inspire high quality evidences via randomized, controlled trials assessing efficacy and safety of CM treatment of CU.

**KEYWORDS** chronic urticaria, Chinese medicine, evidence-based medicine, treatment

Chronic urticaria (CU) is a widespread skin disease and defined as itchy hives that last for at least 6 weeks, with or without angioedema, and that have no apparent external trigger.<sup>(1)</sup> Chronic urticaria can be divided into chronic spontaneous urticaria and chronic inducible urticaria. The condition generally has a prolonged duration of 1 to 5 years and has a significant effect on patients' emotional and physical health-related quality of life. In the United States, patients with CU had impaired mental/physical health and work/non-work activities, similar to moderate-to-severe psoriasis patients.<sup>(2)</sup> Results suggest that better disease management of CU is needed.

Nonsedating second generation H<sub>1</sub>-antihistamines are the current recommendation for initial treatment and are the only agents licensed for use in patients with chronic idiopathic urticaria by evidence-based recommendations. Both guideline from USA and Europe documented that the advantages and disadvantages of each treatment option should be taken into consideration when selecting therapies beyond H<sub>1</sub>-antihistamines.<sup>(3,4)</sup>

Treatment of CU with Chinese medicine (CM) has been shown to relieve symptoms and prevent recurrence, however, the lack of robust evidence from the evidence-based medicine perspective is hindering acceptance of CM by the Western medicine

community and its integration into mainstream healthcare. On the other hand, most of the treatments were reported in Chinese, Korean or Japanese, not in English, during the past decades, which made it hard to be understood by international community. In the recent years, we are delighted to note more and more treatment methods of CU by CM have been reported according to evidence-based medicine.

### Acupuncture

Acupuncture has a long history and been widely used in clinical practice for treating CU in China and other countries. Many clinical studies have reported that acupuncture is effective for the treatment of urticaria.<sup>(5,6)</sup>

A systematic review and meta-analysis of randomized, controlled trials (RCTs) on effectiveness and safety of acupuncture therapy for patients with CU were performed and has been published in English,<sup>(7)</sup> which provide more convincing evidence

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to acupuncture for CU. Six studies with 406 participants were included in the study registered with PROSPERO CRD42015015702. When comparing acupuncture with medications (loratadine, cetirizine), the combined results of 3 RCTs indicated that acupuncture might be more effective than drugs. As an adjunct to medication, the combined results of 3 RCTs suggested that acupuncture plus drugs was superior to drugs in improving overall symptoms. These results indicated that acupuncture might have beneficial effects for the treatment of CU as an adjunct to medication.<sup>(7,8)</sup> These evidence showed that acupuncture might be effective and safe for CU in relieving symptoms.

In CM, acupuncture is believed to function by regulating the balance of qi circulation. In Western medicine, the mechanism of acupuncture is yet not clear. Studies in animals and humans signified that acupuncture can attenuate histamine effect, modulate the function of the immune system and decrease the adhesion molecule.<sup>(9)</sup>

Acupuncture is safe for treating patients with CU, nevertheless, there is only low quality evidence for the effectiveness of acupuncture for CU in relieving symptoms based on the results according to the current evidence. For future research, a consistent measurement for primary outcomes and the quality of research must be improved.

### Herbs

In East Asian regions, by virtue of safety and fewer adverse reaction, a variety of herbal medicines are used in the treatment of CU and they are likely to be a good substitute for Western medicines. Some herbs or herbal formulae have been shown to be effective when applied alone or combined with antihistamines, even when antihistamine did not work alone, with low or high evidence.

In Taiwan area of China, herbs network and core treatments for urticaria were explored by analyzing a nationwide CM doctor's prescription database.<sup>(10)</sup> A total of 97,188 herbs prescriptions were made for 38,514 urticaria patients (99.3% of all CM users), with an average of 5.6 kinds of herbs used per prescription from 628 kinds of herbs. Xiaofeng Powder (消风散, XFP) was the most commonly used in urticaria and nearly all herbs clusters were connected to XFP.

CM doctors often combine XFP with other herbs when treating CU. The anti-allergy effect of XFP is by inhibiting globulin E (IgE) release from mast cells derived from mouse bone marrow cells.<sup>(11)</sup> An earlier report in Taiwan of the 95,765 herbs prescriptions also shows that *Dictamnus dasycarpus Turcz* was the most commonly prescribed single Chinese herb while XFP still was the most commonly prescribed Chinese herbal formula.<sup>(12)</sup> The most commonly prescribed herbal drug combination was XFP plus *Dictamnus dasycarpus Turcz* while the most commonly prescribed triple drug combination was XFP, *Dictamnus dasycarpus Turcz*, and *Kochia scoparia*.

In Korea, doctors are also prescribing a variety of herbal medicines to CU patients in outpatient clinic, and among them, the most-prescribing decoction is Gwakhyangjeonggi-san (GJS), which derived from Huoxiang Zhengqi Powder (藿香正气散) of China. A study to investigate whether GJS actually helps in treating CU was reported by comparing the changes in urticaria activity scores (UAS) at the beginning and at 6 months after completion of the treatment.<sup>(13)</sup> The UAS after 6 months from treatment with GJS was significantly decreased compared to the score before treatment. Nearly half of the patients reported that their symptoms were completely eliminated, and 67% of the patients taking anti-histamines were able to stop it completely. These results shows that GJS improves symptoms of CU and helps patients reduce taking antihistamines.

In Japan, it was reported that cases of CU could be successfully treated with Yokukansan [YKS, Yigan Powder (益肝散)], a traditional Japanese Kampo medicine that proved to ameliorate psychiatric symptoms. Administration of YKS might be a suitable complementary therapy for intractable CU.<sup>(14)</sup> Further, the effect of YKS on mast cells using an *in vitro* system and rat basophile leukemia (RBL-2H3) cells are investigated, which show that YKS inhibited secretion of beta-hexosaminidase, intracellular calcium increase, production of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and intercellular adhesion molecule-1 (ICAM-1) expression, and that several YKS ingredients may be the key effectors. Its dual inhibitory action on TNF- $\alpha$  release from mast cells and subsequent endothelial ICAM-1 expression on endothelial cells, in addition to its inhibitory potential to degranulation of mast cells, may explain the benefit

of using YKS for a certain population of patients with chronic urticaria.<sup>(15)</sup>

While in China mainland, a study to investigate the clinical efficacy of herbal decoction *Radix Astragali Mongolici*, *Fructus Jujubae*, *Rhizoma Dioscoreae Oppositae*, *Poria*, *Radix Angelicae Sinensis*, prepared *Radix Polygoli Multiflori* and Western medicine (cetirizine 10 mg/d) for 8 weeks of treating CU patients was performed.<sup>(16)</sup> The gray similar degree of correlation analyses, association algorithm and genetic algorithm in data mining were adopted to analyze the effects of herbs decoction and cetirizine in 60 CU patients. Herbs decoction had a better effect at a later stage, whereas cetirizine was better in the early stage. The duration of the disease course had an impact on the effect of treatment. If the average total symptom score before treatment is  $\leq 83.0036$ , herbal decoction or cetirizine treatment can achieve better efficacy.

Although more herbs than listed above were applied in East Asia countries, less evidence-based report could be found. Novel study methods to analyze and summarize this body of clinical data and English publication are urgently needed to translate CM into modern science.

### Food

A therapeutic approach in CU is the identification and elimination of the underlying causes and/or eliciting triggers.<sup>(1)</sup> In China, food avoidance is common among patients with CU because food allergy is considered to be the cause of disease. The foods considered allergenic include fish, shellfish, beef, lamb, egg and spicy foods. Patients choose to eliminate these possible allergic foods from their diet without further diagnostic procedures.

However, a recent report in China shows that among 341 patients, CU induced by food allergy was found in only 2.8% of patients. The most common food allergens detected in this study were soy and peanut (10%), beef, lamb and chicken (5%), and crab and shrimp (4%).<sup>(17)</sup> Foods avoided do not correspond to serum food-specific IgE. The incidence of IgE-mediated urticaria, as demonstrated by open food challenge, is low. Food avoidance was found ineffective in 83% of patients, indicating that dietary restriction based on the assumption of food allergy was unnecessary and would not lead to clinical remission. Physicians and patients

should be aware of unnecessary dietary avoidance while seeking treatment of CU.

### Future Direction

Although some progress in CM treatment of CU have been made in recent years, including acupuncture, herbs and food issues, many issues surrounding the efficacy and safety of CM use in CU treatment remain unresolved and these hinder the potential benefits of CM from being safely and effectively harnessed. High quality evidences via RCTs assessing efficacy and safety of CM treatment of CU are needed for the traditional practice to gain acceptance by Western medical practitioners and become an integral component of the healthcare system.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### Authors Contributions

Wang YM and Du L carried out data collection, interpretation and drafting of the manuscript. Zhu YJ carried out design and revising of the manuscript content. All authors read and approved the final manuscript.

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