

Nettle Allergy: a Review and Clinical Perspective

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Abstract

Purpose of review Stinging nettle (*Urtica dioica*) is a common cause of contact urticaria worldwide; however, its clinical relevance in allergic rhinitis and aeroallergen immunotherapy has not been well established. This presents a clinical conundrum to the physician and can potentially impact the effectiveness of treatment of allergic rhinitis in nettle sensitized patients. The objectives of this article are to review the available literature regarding the geographic distribution of nettle, allergen(s) involved, cross-reactivity, role in allergic rhinitis, immunotherapy efficacy, and provide a clinical perspective on the evaluation and treatment of nettle sensitized patients.

Recent findings Stinging nettle (*Urtica dioica*) is a bi-annual pollinator with worldwide distribution and wide use in homeopathy. Limited data suggest that nettle pollen allergens may be considered clinically relevant and that nettle pollen allergy may be underestimated. More recent allergomic analysis of nettle pollen has revealed protein allergens including an osmotin and a pectin esterase which may implicate cross-reactivity with other pollens and foods. One study describes in vivo nettle immunotherapy.

Summary Overall, there is a paucity of medical literature evaluating the role of nettle in allergic rhinitis with even fewer studies assessing the clinical efficacy of nettle immunotherapy. Cross-reactivity patterns with other pollens and foods remains to be fully elucidated. Given the immense medical and economic impact of allergic rhinitis and the worldwide distribution of nettle, prospective randomized controlled trials are needed to evaluate the possible contribution of nettle allergy and efficacy of nettle immunotherapy.

Introduction

Allergic rhinitis is a common diagnosis that affects up to 30% of the US population and is increasing in prevalence throughout the USA and other Westernized countries [1, 2]. Studies have demonstrated that allergic

rhinitis significantly impairs health-related quality of life and is responsible for billions of dollars in medical spending and impaired work productivity [3, 4]. Given this immense burden, improvement in treatment modalities for allergic rhinitis will have significant medical and economic impact. It also appears that a greater understanding of allergens involved may facilitate in the appropriate treatment of allergic rhinitis.

Nettle is a group of herbaceous weeds that belong to the family Urticaceae (Table 1). Urticaceae include five prominent members: *Urtica* (stinging nettle), *Boehmeria* (false nettle), *Parietaria* (pellitory), *Pilea* (clearweed, richweed), and *Laportea* (wood nettle) [5].

Nettle is originally from Northern Europe and Asia but is now found worldwide to include temperate and tropical areas [5, 6, 7]. It has even been documented in the Himalayas at altitudes of over 3000 m [6]. In the USA, nettle is widely distributed and is found in every state except Hawaii [8]. It is a

wind-pollinated (anemophilous) perennial plant that flowers in the summer and autumn months, although stinging nettle may flower as early as January or February in southern latitudes [5, 6, 7].

The genus name of stinging nettle, *Urtica*, comes from the Latin verb *urere*, meaning “to burn,” which describes the stinging hairs classically known to cause contact dermatitis [5, 6, 9]. *Dioica*, the species name of stinging nettle, means dioecious and describes the plant as either male or female [7].

Urtica dioica is identified by leaves that are green, simple, cordate, pointed, coarsely toothed, and have characteristic stinging hairs on the stem and underside of the leaves (Fig. 1) [6, 7, 10]. Nettle pollen grains are small (12–15 µm), oblate-spheroidal to spheroidal, and 2–4-porate [5].

From henceforth in this review, unless otherwise specified, stinging nettle will be referred to as ‘nettle’.

Evidence in homeopathy

Nettle has long been used as a homeopathic medicinal herb in many countries worldwide [7]. Intravenous, oral, and topical preparations have been described to treat a variety of ailments such as hay fever, eczema, rheumatoid arthritis, osteoarthritis, gout, benign prostatic hypertrophy, urinary tract infections, neuralgia, bleeding, malignancy, and others [6, 7, 9, 11, 12, 13].

The chemical components of nettle are numerous and include acetylcholine, histamine, serotonin, leukotrienes, formic acid, flavonoids, tannins, carotenoids, vitamins B, C, and K, essential oils, and others [6, 13, 14, 15]. These chemical components have been suggested to demonstrate various

Table 1. Classification of stinging nettle. Adapted from <https://plants.usda.gov/core/profile?symbol=URDI> Accessed 21 Jun 2018. USDA, NRCS. 2017. The PLANTS Database (<http://plants.usda.gov>, 13 December 2017). National Plant Data Team, Greensboro, NC 27401-4901 USA

Kingdom	Plantae	Example
Subkingdom	Tracheobionta	Vascular plants
Superdivision	Spermatophyta	Seed plants
Division	Magnoliophyta	Flowering plants
Class	Magnoliopsida	Dicotyledons
Order	Urticales	
Family	Urticaceae	Nettle family
Genus	<i>Urtica</i> L.	Nettle
Species	<i>Urtica dioica</i> L.	Stinging nettle

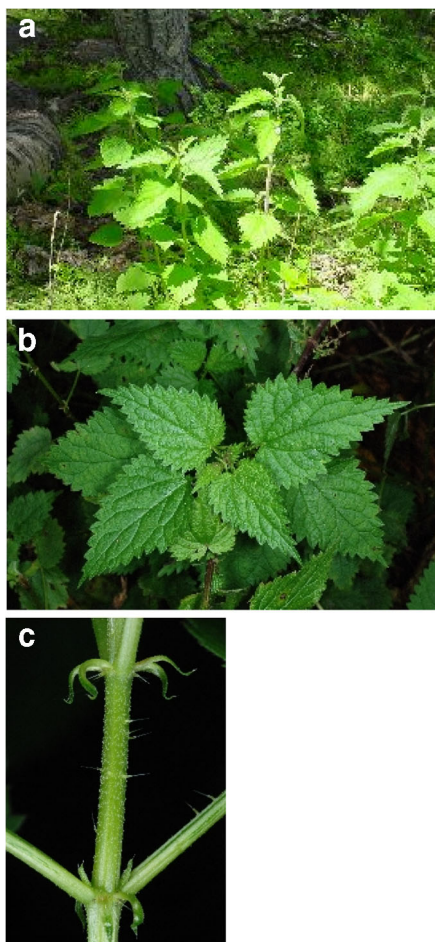


Fig. 1. Stinging nettle (a–c). Courtesy of Patrick J. Alexander, hosted by the USDA-NRCS PLANTS Database. <https://plants.usda.gov/core/profile?symbol=URDI> Accessed 21 Jun 2018. USDA, NRCS. 2017. The PLANTS Database (<http://plants.usda.gov>, 13 December 2017). National Plant Data Team, Greensboro, NC 27401-4901 USA.

pharmacological activities, such as anti-inflammatory, anti-hemorrhage, anti-bacterial, antiviral, immunomodulatory, anticancer, diuretic, cardiovascular, and antioxidant effects associated with scavenging of free radicals or reactive oxygen species [6, 7, 13]. Riehemann et al. suggest that nettle leaf extract suppresses the NF- κ B pathway via preventing degradation of I κ B- α , contributing to an anti-inflammatory effect and hence a possible therapeutic agent in rheumatoid arthritis [11]. Conversely, Franciskovic et al. describe MyD88 and NF- κ B stimulation caused by nettle extract [16•].

Evidence in allergic disease

Nettle is the most common cause of contact urticaria worldwide and has been postulated as a cause of allergic rhinitis and systemic anaphylaxis. The mechanism of action of contact urticaria is thought to be both biochemical and mechanical [10, 17]. Contact of the skin with needle-like-hairs on the plant's

leaves results in direct impalement of spicules and inoculation of the skin with acetylcholine, histamine, serotonin, leukotrienes, formic acid, butyric acid, and other irritants [10, 14, 17, 18]. Typically, this results in a local wheal and flare reaction however a case report by Khan in 2003 postulated that the direct inoculation of histamine and other irritants may have resulted in systemic anaphylaxis in one patient [17].

A study of 51 Eastern Polish herb processing workers evaluated nettle (among other herbs) in the setting of work-place rhinopulmonary symptoms [19]. Twenty-six percent of workers felt their symptoms were related to nettle exposure. The frequency of positive intradermal skin tests to 0.1 mL of nettle extract in symptomatic patients was statistically significant ($p < 0.05$). The authors suggest appropriate preventive measures should be considered for industrial processing of nettle [19].

In 2009, a prospective study comparing the performance characteristics of skin testing and ImmunoCAP (Phadia AB, Uppsala, Sweden) in 250 adult patients with chronic rhinitis, 25.1% of patients showed sensitization to nettle with skin testing and 25.9% with ImmunoCAP [20]. This study did not evaluate the clinical relevance of the sensitization.

In 2016, Tiotiu and colleagues studied two patients with seasonal rhinoconjunctivitis symptoms from May to September (nettle flowering and pollination period) in France [21••]. One patient demonstrated monosensitization to nettle pollen on skin prick test, positive nasal provocation test, and positive basophil activation test. The second patient demonstrated polysensitization, with the strongest skin test reaction being to nettle pollen extract. Interestingly, this patient is described to have developed anaphylaxis after exercise, 2 h after ingestion of nettle soup and other foods. Tiotiu concluded that nettle pollen allergens should be considered clinically relevant and that nettle pollen allergy is likely underestimated (due to overlap with grass season in France).

Nettle allergens and cross-reactivity

Nettle allergens that may be relevant in allergic disease have recently been described. In 2016, Tiotiu et al. characterized four basic protein allergens of *Urtica dioica* through allergomic analysis [21••]. Among the protein allergens evaluated were an osmotin and a pectin esterase.

Osmotin proteins are stress responsive plant antifungal proteins [21••, 22]. They are thaumatin-like protein allergens and belong to the pathogenesis-related 5 (PR-5) protein family, both of which have been implicated in food allergy and pollen-food allergy syndrome [21••, 22, 23, 24]. Sharma et al. reported that osmotin showed significant sequence identity with allergens of the PR-5 protein family. The authors therefore suggest possible cross-reactivity of osmotin with allergens of the PR-5 protein family, such as tomato, kiwi, apple, and bell pepper [22]. The clinical significance of this possible cross-reactivity remains to be determined (Table 2).

Tiotiu et al. report that it is not known whether osmotin or other nettle allergens are involved in food-dependent exercise-induced anaphylaxis, and suggest further investigation is needed [21••]. Osmotin is used in various stages of development of genetically modified crops, although the allergenicity of osmotin in this setting is also unknown [21••, 22].

Table 2. Hypothesized cross-reactivity patterns of nettle with other plants and foods that contain an osmotin or pectin methyltransferase allergen. Nettle and pellitory demonstrate little (if any) cross-reactivity which does not appear to be clinically relevant

Common name	Scientific name	Antigen	Possibly cross-reactive with nettle	Not cross-reactive with nettle
Pellitory	<i>Parietaria judaica</i>	Par j		x
Japanese hop	<i>Humulus japonicus</i>	Hum j	x	
Tomato	<i>Solanum lycopersicum</i> *	Sol I*	x	
Apple	<i>Malus domestica</i>	Mal d	x	
Bell pepper	<i>Capsicum annum</i>	Cap a	x	
Kiwi	<i>Actinidia deliciosa</i>	Act d	x	
Olive	<i>Olea europaea</i>	Ole e	x	
Oriental plane	<i>Platanus orientalis</i>	Pla o	x	
Russian thistle	<i>Salsola kali</i>	Sal k	x	
Birch	<i>Betula verrucosa</i>	Bet v	x	

*Previously known as *Lycopersicon esculentum* (Lyc e)

Pectin esterases, a main component of the plant cell wall, have been implicated as pollen allergens [21••, 25, 26]. Mahler et al. demonstrated that Bet v 8, a birch pollen allergen, and plant pectin esterases have highly homologous amino acid sequences [25]. They concluded that Bet v 8 may share IgE epitopes with unrelated allergen sources and therefore may be implicated in clinically relevant cross-reactivity. Pectin methylesterases have also been implicated as food allergens, such as in kiwi fruit [26].

It appears that little, if any, cross-reactivity has been demonstrated between nettle pollen and *Parietaria* (also of the family Urticaceae), which are well known in the Mediterranean region for their role in allergic rhinitis [21••, 27, 28, 29, 30]. Corbi et al. reported in 1985 a weakly allergenic cross-reactivity between nettle and four *Parietaria* pollens despite common antigenic determinants [27]. In 1988, Holgate et al. reported that 13 of 62 patients were skin test reactive to nettle but there was no correlation between skin test reactivity to nettle and *Parietaria* [28]. In 2006, Vega-Maray et al. reported that Par j 1, the major allergen of *Parietaria judaica* pollen, is not present in *Urtica dioica* pollen despite being members of the same family [29].

In a Korean study of 260 patients sensitized to Japanese hop pollen, a statistically significant association was noted on skin prick test to nettle and sunflower pollen ($p < 0.05$) [31]. The authors recommended further laboratory investigations to identify any cross-allergic components.

Immunotherapy

There is a paucity of clinical studies evaluating the efficacy of nettle immunotherapy. In 1990, Mittman et al. performed a randomized, double-blind study of 69 patients with allergic rhinitis symptoms [15]. Patients received 600 mg of freeze-dried nettle leaf powder by mouth or

placebo at onset of symptoms. Fifty-eight percent of patients receiving freeze-dried nettle leaf powder compared to 37% of patients receiving placebo noted symptom improvement.

In 2009, Roschek et al. performed *in vitro* studies with a proprietary nettle extract and reported histamine H₁ receptor inactivation, tryptase inhibition, COX-1 and -2 inhibition, and inhibition of prostaglandin D₂ production [9]. They proposed that these effects likely contribute to the anti-inflammatory nature of nettle and possible role in the treatment of allergic rhinitis.

Despite the unknown efficacy of nettle immunotherapy, nettle extract is used in immunotherapy prescriptions. The United States Army Centralized Allergen Extract Laboratory (USACAEL) reported that nettle extract was included in 3999 of 142,428 (2.8%) aeroallergen immunotherapy prescriptions ordered between 2013 and 2017 (Susan Kosisky, Chief Microbiologist at USACAEL, personal communication). Ultimately, more randomized controlled trials are needed to evaluate the effectiveness of nettle immunotherapy.

Evaluation and treatment considerations

Allergists are faced with patients presenting with a variety of allergy symptoms and tasked to identify a culprit (if any) and to provide treatment strategies to reduce symptoms. Obtaining an accurate and informative history becomes crucial in this evaluation, which can be nebulous and confounding. Consideration for nettle allergy may be taken in patients with contact urticaria, rhinitis, rhinoconjunctivitis, seasonal asthma symptoms, idiopathic anaphylaxis, and exercise-induced anaphylaxis. For patients in whom nettle allergy is possible, the Allergist may consider focusing the history on seasonality of symptoms, nettle exposure including environmental exposure, use in homeopathic remedies and in food preparation, association with exercise or exertion, and other exposures which may be confounders (i.e., grass season, co-ingestion of another food, etc.). Cross-reactivity patterns have not been well established, thus it is not suggested to focus the history taking on this.

Identifying a culprit allergen provides a target for avoidance counseling, the primary treatment strategy in IgE-mediated hypersensitivity. Commercial nettle extract, which theoretically contains nettle antigens including an osmotin and/or pectin esterase, has historically produced a wheal-and-flare on skin testing and in select patients appears to correspond to symptoms. Nettle serum-specific IgE also appears to be complementary to skin testing. If nettle allergy is possible, specific IgE testing by skin testing or serology is recommended.

Not all allergens, however, are completely avoidable. For example, nettle has worldwide distribution and in some cultures is utilized in food preparation. The Allergist often must then consider alternative treatment strategies. If nettle allergic rhinitis or rhinoconjunctivitis is considered, standard medical therapy with antihistamines, intranasal glucocorticoids, leukotriene modifying agents, and FDA-approved

adjunctive pharmacotherapies are recommended. If the patient desires immunotherapy, a risk versus benefit discussion for inclusion or exclusion of nettle extract is recommended given lack of efficacy data. If nettle anaphylaxis is considered, in addition to providing avoidance strategies, the patient should be prescribed an epinephrine autoinjector and instructed on its use. Given lack of safety and efficacy data, nettle immunotherapy is not recommended in patients with histories suspicious for nettle anaphylaxis.

Conclusion

Overall, there is a paucity of medical literature evaluating the role of nettle in allergic rhinitis with even fewer studies assessing the clinical efficacy of nettle immunotherapy. Most of the literature is limited to case reports, surveys, questionnaires, and retrospective data. Given the immense medical and economic impact of allergic rhinitis and the worldwide distribution of nettle, prospective randomized controlled trials are needed to evaluate the possible contribution of nettle allergy and efficacy of nettle immunotherapy. In addition, it appears that nettle may not demonstrate cross-reactivity with the closely-related and allergenic *Parietaria*, however cross-reactivity patterns with other pollens and foods, including possible implication in systemic anaphylaxis, remains to be fully elucidated. Future research should aim to further characterize nettle allergens and cross-reactivity. With improved understanding of the role of nettle in allergic rhinitis, allergens involved, and clinical efficacy of nettle immunotherapy, physicians can provide patients with evidence-based recommendations regarding use of nettle immunotherapy.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no competing interests.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer

The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force or the Department of Defense.

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