Alternative products to treat allergic rhinitis and alternative routes for allergy immunotherapy

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ABSTRACT

Background: *Some alternative products instead of immunotherapy are used in patients with allergic rhinitis (AR).*

Methods: *In this paper, alternative products to treat allergic rhinitis and alternative routes for allergy immunotherapy are reviewed.*

Results: *Alternative products and methods used instead of immunotherapy are tea therapy, acupuncture,* Nigella sativa, *cinnamon bark, Spanish needle, acerola, capsaicin (*Capsicum annum*), allergen-absorbing ointment, and cellulose powder.* N. sativa *has been used in AR treatment due to its anti-inflammatory effects.* N. sativa *oil also inhibits the cyclooxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism. The beneficial effects of* N. sativa *seed supplementation on the symptoms of AR may be due to its antihistaminic properties. To improve the efficacy of immunotherapy, some measures are taken regarding known immunotherapy applications and alternative routes of intralymphatic immunotherapy and epicutaneous immunotherapy are used.*

Conclusion: *There are alternative routes and products to improve the efficacy of immunotherapy.*

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Aeroallergen immunotherapy (AIT) works by stimulating dendritic cells (DC), T cells, and B cells. By contrast, adverse effects are mediated by mast cells and blood vessels. The ideal route for AIT is characterized by a high density of DCs, T cells, and B cells but a low density of mast cells and blood vessels. Lymph nodes contain masses of DCs, T cells, and B cells but few mast cells. Intralymphatic AIT (ILIT) was shown to be safe, and the number of allergen injections could be reduced to three. The epidermis contains dense DCs and no mast cells or blood vessels. Epicutaneous AIT (EPIT) was also shown to be safe, and the allergen administrations could be reduced to six patches.[1]

The number of allergen administrations can be reduced by enhancing the immunologic effects of each administration. AIT works by inducing blocking antibodies, T-helper 1 and regulatory T cells, orchestrated by DCs. Immunologic effects are classically enhanced by adjuvants. Replacing alum with bacterial products, such as the lipopolysaccharide derivative monophosphoryl lipid A or bacterial DNA, allows for a reduction in the number of injections to four or six.[1,2–4]

Alternative medicine refers to nontraditional medical care used instead of mainstream medical care. Some alternative products are used in patients with AR. Alternative products and methods used for treatment of AR are tea therapy, acupuncture, and *Nigella sativa* Linn. (Ranunculaceae), Cinnamon bark, Spanish needle, and acerola; capsaicin (*Capsicum annum*), allergen-absorbing ointment and cellulose. Alternative routes of immunotherapy have been studied, including ILIT and EPIT. This article reviewed novel alternative routes of allergy immunotherapy administration as well as the use of alternative medicine products for the treatment of allergic diseases.

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ALTERNATIVE ROUTES

ILIT

In lymph nodes, the density of DCs, B cells, and T cells is maximal, whereas the density of mast cells is low. Direct injection into a subcutaneous lymph node has been shown to be safe and to ameliorate symptoms of AR after three injections.[1] ILIT aims to improve treatment efficacy and safety, and to reduce treatment duration, which, thereby, makes allergen immunotherapy more patient friendly. In different studies, ILIT was administered three times at 4-week intervals.[5,6] ILIT with grass-pollen or birch-pollen extracts seems to reduce nasal allergic symptoms. Senti *et al.*[7] showed that ILIT was safe and induced allergen tolerance after three injections in a randomized double-blind trial ILIT with Modular-Antigen-Translocation-Feld 1 (cat antigen) in alum. Hence, ILIT might constitute a less time-consuming and more cost-effective alternative to conventional subcutaneous allergen-specific immunotherapy.[6] Through injection into a lymph node, it is hoped that ILIT will enhance the development of protective immunity.[8,9] Clinical trials conducted to date demonstrated that ILIT may be clinically effective after only a few injections and induces allergen-specific immunoglobulin G as demonstrated with subcutaneous immunotherapy.[10,11]

EPIT

The epidermis is characterized by a high density of potent DCs and an absence of blood vessels. Therefore, AIT administered *via* this route should be more efficient and safer. EPIT has been demonstrated to be safe and to ameliorate the symptoms of AR after six allergen patch applications.[1] In EPIT, an allergen is administered to the non-vascularized epidermis.[12] However, as an advantage of EPIT over sublingual immunotherapy, keratinocytes can additionally be activated by physical irritation, *e.g.*, abrasion or adhesive tape stripping, or by adding adjuvants.[13] Epithelial damage increases the keratinocyte expression of additional molecules of interleukin (IL) 1α, IL-6, and tumor necrosis factor α, skewing the immune response toward a [T-helper type 1] type response.[14] Such activation of keratinocytes is important to create a proinflammatory environment with enhanced activation of Langerhans cells.

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Besides enhancing the penetration of allergens by removing the stratum corneum,[15] "repeated tape stripping also functions as a 'physical' adjuvant through the activation of keratinocytes, which then secrete various proinflammatory cytokines (IL-1, IL-6, IL-8, [tumor necrosis factor] α and [interferon] γ), which favor the maturation and emigration of DCs to the draining lymph nodes."[16,17] The results of the first pilot trial revealed that patients treated with 12 patches that contained pollen extract showed significant alleviation of hay fever symptoms compared with patients who received placebo. In line with the historic study results described above, no severe systemic allergic reactions were reported. The only adverse events observed were mild local eczematous reactions under the skin patch.[18]

EPIT holds promise in all four aspects: (1) the epidermis contains a high number of potent antigen presenting cells, (2) adjuvants can be topically administered and/or physical or chemical trauma to keratinocytes may already act as a physical adjuvant, (3) the epidermis is nonvascularized and it decreases systemic exposure to allergen and thus decreases the risk of a systemic reaction, and (4) epicutaneous administration can be performed at home and is painless.[12]

ALTERNATIVE PRODUCTS AND METHODS

Tea Therapy

In Asia, tea therapy is an easy-to-administer self-care method for patients with AR. Japanese green tea with methylated catechin as an active ingredient is thought to be beneficial for patients with AR who are sensitized to cedar and to relieve symptoms, improve quality of life, and reduce the peripheral eosinophil count.[19] Benifuuki green tea contains O-methylated epigallocatechin-3-O-(3-O-methyl) gallate, a compound that has antiallergy properties.[20–22]

Acupuncture

Acupuncture can be recommended as an adjunctive therapy for AR. Acupuncture and acupressure work *via* stimulating specific points on the human body.[19] Based on the latest meta-analysis of studies published from 1980 to 2013, acupuncture seems to be a safe, valid, and cost-effective option for allergy relief, and can be recommended as an adjunctive therapy for AR.[23] Acupuncture decreases nasal symptom scores and improves quality of life with no serious systemic reaction or adverse effects. Its efficiency and safety heavily depend on the clinical experience and skill of the acupuncturist.[19,23] Zhang *et al.*[24] investigated the efficacy and safety of ear acupressure (EAP), which is a noninvasive semi–self-administered form of acupuncture, in perennial AR (PAR). Participants with PAR were randomized to receive real or sham EAP treatment once a week for 8 weeks and then were followed-up for 12 weeks. The participants were instructed to administer EAP stimulation three times daily. They concluded that EAP showed short-term and extended benefit for improving PAR symptoms and quality of life for patients with PAR. [24]

Herbal Products for AR

N. sativa. The seeds of *N. sativa*, commonly known as black seed or black cumin, are used in folk (herbal) medicine throughout the world for the treatment and prevention of several diseases and conditions, which include asthma, diarrhea, and dyslipidemia.[25] The seeds contain fixed and essential oils, proteins, alkaloids and saponin. Much of the biologic activity of the seeds has been shown to be due to thymoquinone, the major component of the essential oil, but the activity is also present in the fixed oil.[25] *N. sativa* has antiallergic, antioxidant, and anti-inflammatory effects on patients with allergy. Furthermore, *N. sativa* shows beneficial effects on asthma.[26] Boskabady *et al.*[27] reported the antiasthmatic (bronchodilatory) effect of boiled extract of *N. sativa* in the airways of patients with asthma. *N. sativa* (black seed) is capable of relieving the symptoms of allergic diseases (AR, atopic eczema, bronchial asthma).[28]

Effects of N. sativa on AR. In the prospective, double-blind clinical trial of patients with AR by Nikakhlagh *et al.*,[29] *N. sativa* was reported to reduce the presence of nasal mucosal congestion, nasal itching, runny nose, sneezing attacks, turbinate hypertrophy, and mucosal pallor during the first 2 weeks. In a study by Kalus *et al.*,[28] they reported that black seed oil was an effective adjuvant for the treatment of allergic diseases (AR, bronchial asthma, atopic eczema). Işık *et al.*[30] reported that *N. sativa* seed supplementation during specific immunotherapy for AR may be considered a potential adjuvant therapy. The beneficial effects of *N. sativa* seed supplementation on the symptoms of AR may be due to its antihistaminic properties.[30] Chakravarty[31] demonstrated that, when rat macrophages were incubated with nigellone thymoquinone (a carbon polymer) obtained from *N. sativa* seed, nigellone inhibited histamine release from macrophages.

Cinnamon Bark, Spanish Needle, and Acerola. The botanical product that is a combination of cinnamon bark extract, dehydrated Spanish needle (*Bidens pilosa*) leaf and stem, and acerola fruit concentrate inhibits prostaglandin D_2 and shows a steroid-like effect. It decreases allergic inflammation in the late phase.[32,33]

Capsaicin. Capsaicin (*C. annum*), derived from red peppers, may work by desensitizing nasal nerve fibers and reducing nasal hyperresponsiveness.[32,34] It helps to improve nasal congestion and is commercially available.[35]

Allergen-Absorbing Ointment. Petroleum-based ointment that contains long-chain hydrocarbons can block allergen absorption into the nasal mucosa. When applied three times daily for 14 days, nasal symptom scores improved in both adults and children.[33,36–38]

Cellulose Powder. Inert and micronized cellulose powder has been speculated to block mucosal allergen absorption after intranasal application.[33]

Other Herbal Preparations. There are some other herbal preparations that have shown limited efficacy or a lack of efficacy in the treatment of AR and/or conjunctivitis. These are quercetin (bioflavonoids),[39] stinging nettle (*Urtica dioica*) (radix urticae),[40] *Perilla frutescens* (an Asian herb),[41] Eucalyptus (generates an oil rich in 1,8-cineole),[42] and grape seed extract.[43]

CONCLUSION

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