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REVIEW

Global Ragweed Allergy: Molecular Allergens and Integrated Control Strategies

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Abstract: Originally native to North America, ragweed has become a pervasive invasive species worldwide over the past century, posing a substantial public health risk as a potent allergen. This review explores the key allergens found in common ragweed, assesses global trends in ragweed sensitization, particularly in China, and examines various therapeutic and biological control methods. There are currently 11 identified ragweed allergens, with Amb a 1 and 11 recognized as the primary triggers. Epidemiological data indicate higher rates of sensitization in North America and Europe, with a growing trend observed in China. Ragweed-induced type I hypersensitivity typically presents as seasonal allergic rhinitis, conjunctivitis, and asthma symptoms. Strategies for managing ragweed allergy include allergen avoidance, pharmacotherapy, and allergen immunotherapy (AIT). Biological control using *Ophraella communa* and *Epiblema strenuana* effectively limits ragweed proliferation. Accurate allergen identification and personalized treatment can significantly reduce the health burden associated with ragweed. An in-depth understanding of ragweed sensitization patterns and biological control measures is essential for the long-term prevention of ragweed allergies.

Keywords: ragweed, molecular allergen, allergic rhinitis, allergic asthma, biological weed control

Introduction

Ragweed is an annual flowering plant belonging to the *Ambrosia* genus, which comprises around 40 species in the Asteraceae family. *Ambrosia artemisiifolia* L., commonly known as common or short ragweed, is the most widespread and problematic species, primarily responsible for allergic reactions. Other invasive ragweed species, such as *A. trifida* L. (giant ragweed) and *A. psilostachya* DC. (western ragweed), are also widely distributed across several continents alongside *A. artemisiifolia* L. Originating in North America, ragweed is a major cause of pollen allergies in both North America and Europe. Its spread in several Asian countries, including China, Korea, and Japan, has been influenced by factors like urbanization, climate change, and long-distance transportation. Ragweed sensitization rates in China, in particular, are rising steadily each year. To date, 11 allergens have been identified in ragweed, with Amb a 1 and Amb a 11 being the major allergens. Component-resolved diagnosis (CRD) has improved the accuracy of detecting specific sensitizations and potential cross-reactivity.

Ragweed pollen, particularly abundant from August to October, triggers type I hypersensitivity, contributing significantly to hay fever, and is associated with allergic rhinitis, conjunctivitis, and asthma. Allergen immunotherapy (AIT), including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), is a proven long-term treatment for ragweed sensitization. During peak pollen season, pharmacological treatments such as antihistamines, mast cell stabilizers, and corticosteroids help alleviate symptoms. Recently, biological agents have emerged as promising treatments for moderate-to-severe allergic conditions. Additionally, biological weed control is essential for reducing the long-term impact of ragweed allergies.

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This review examines the allergens in common ragweed, highlights global sensitization patterns, especially in China, and discusses treatment options and biological control strategies for managing ragweed.

Prevalence of Ragweed Sensitization

Ragweed, originally from North America, is widely distributed across the United States and Canada. Since the 19th century, it has spread to Europe through global trade, often as a contaminant in grains and seeds. Its strong adaptability and high pollen production have enabled it to be established in numerous European countries. Factors like rising temperatures, increased carbon dioxide levels, and urbanization have further driven its invasiveness and global spread. In addition to North America and Europe, ragweed has been documented in Asia, South America, Australia, and Africa.[1,2]

The prevalence of ragweed sensitization varies globally (Figure 1 and Table 1), with rates generally higher in North America and Europe compared to other regions. In the United States, the NHANES III survey reported a 26.2% sensitization rate in the general population, while NHANES 2005–2006 found rates between 23.0% and 32.8% among those with allergic symptoms.[3,4] In Canada, a study across six locations showed a sensitization rate of about 15.3% in the general population, with regional variation.[5] In Europe, an estimated 23.2 million people are affected by ragweed allergies, and 15.8 million have clinically significant sensitization.[6] A multicenter study across 14 European countries found that 66.8% of allergic patients reacted to ragweed, though rates varied by country.[7] Areas with high ragweed pollen levels include southwestern Russia, southern and eastern Ukraine, the Pannonian Plain in Central Europe, France's Rhone-Alpes region, and Italy's Po River Valley.[8] Sensitization rates in Hungary (Szeged, Budapest), Italy (Magenta), Serbia (Vranje), France (Rhone), Bulgaria (Sofia), and Croatia (Ivanić Grad) exceeded 50%,[6] with Hungary's Szeged region reaching 84.8% prevalence.[9] In contrast, countries like Belgium, Finland, Ireland, Norway, and Spain report low sensitization rates below 5%.[6]

In China, ragweed pollen concentrations peak in August and September, with sensitization rates rising in northern regions. A seven-year study in Beijing observed a steady increase in ragweed sensitization rates, underscoring the need for control efforts within urban environments.[10]

Ragweed pollen allergy is concentrated in northern China. In Beijing, 14.68% of allergic patients had detectable specific immunoglobulin E (sIgE) to ragweed, and 78% of those sensitized to weed pollen showed reactivity to ragweed.[10,23] Other studies indicate that 19% of allergic rhinitis (AR) patients in Taiyuan, Shanxi Province,[24] and 3.7% of allergic individuals in Tangshan City, Hebei Province, are sensitized to ragweed, with many cases showing IgE-

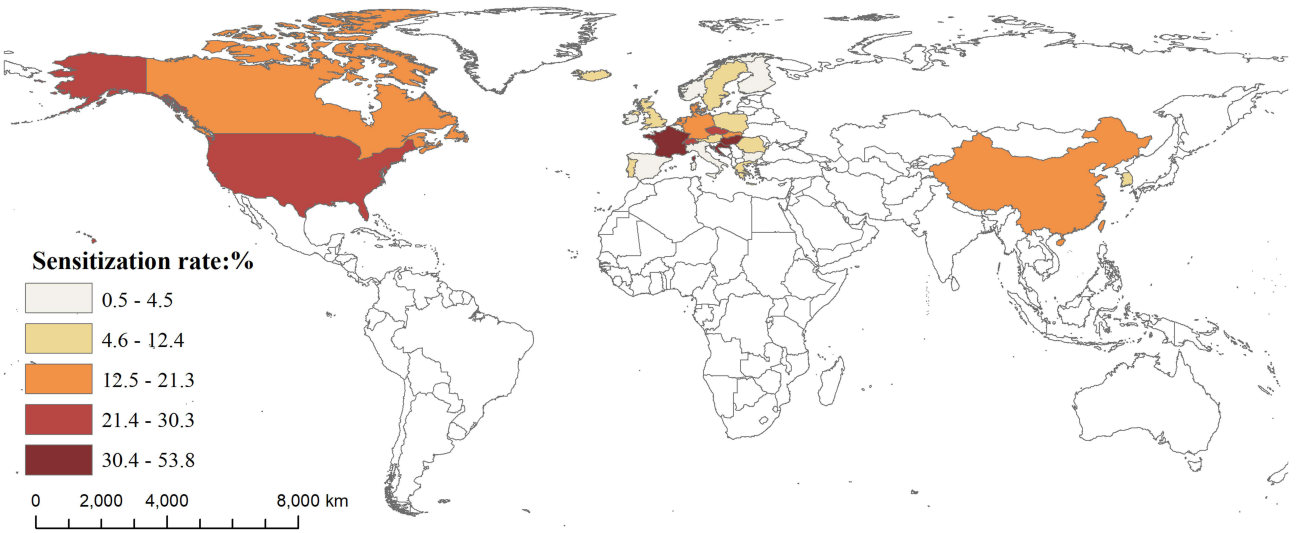

Figure 1 Global ragweed sensitization rates. There is a positive correlation between the darkness of the area and the prevalence of ragweed allergy, with darker regions indicating higher levels of ragweed allergy presence.

Table 1 Global Ragweed Sensitization Rates[3,5,10–22]

Country	Sensitization Rate (%)
Hungary	53.8
France	46.2
Croatia	39.2
Switzerland	30.3
United States	26.2
Czech Republic	23.0
Slovakia	21.3
Germany	19.5
Netherlands	18.6
Denmark	17.1
Canada	15.3
China	14.7
Portugal	12.4
Greece	11.7
Poland	10.8
Romania	9.3
Korea	8.7
Austria	8.5
UK	7.9
Iceland	6.5
Sweden	5.7
Italy	4.5
Ireland	3.7
Belgium	3.0
Finland	2.3
Spain	1.7
Norway	0.7
Bulgaria	0.5

mediated cross-reactivity with mugwort (*Artemisia*), the dominant autumnal allergen in northern China.[25] In Dongying City, Shandong Province, 14.78% of allergic patients had detectable ragweed sIgE.[26]

Southern China has limited data on ragweed sensitization. In Guangdong Province, 40.6% of weed pollen-sensitized patients reacted to ragweed,[27] though only 7.5% tested positive reaction to Amb a 1 in a CRD analysis. Unlike northern China, where ragweed allergy is linked to cross-reactive carbohydrate determinants (CCDs) rather than mugwort, southern regions show stronger CCD-related ragweed sensitization.[27]

The distribution of ragweed in China does not always match high-prevalence sensitization areas. Much of the observed ragweed sensitization in northern China may result from cross-reactivity with the mugwort. Ragweed is found in over 23 provinces, especially in East China, [28,29] which has significant trade routes with the United States, facilitating ragweed seed dispersal in urbanized areas. [30,31]

However, in China, ragweed allergy is primarily observed in northern regions and is largely due to cross-reactivity with mugwort, which is the dominant allergenic pollen in autumn. A recent study across 13 cities in northern China confirmed that mugwort is the main autumnal allergen, with ragweed only being predominant in Shenyang. [32] Cross-reactivity between mugwort and ragweed is largely due to similarities in certain allergens. [33–35] Research in northern China found that 46.9% of individuals with specific IgE antibodies were sensitized to Art v 1 (mugwort), while only 11.2% were sensitized to Amb a 1 (ragweed). Almost all individuals sensitized to ragweed were also sensitized to mugwort, with significantly elevated IgE levels, and no cases of mono-sensitization to ragweed were identified.[25] Another study in western China found that approximately 36% of children sensitized to mugwort with respiratory allergies also showed cross-reactivity to ragweed, while only 13.9% had specific IgE for Amb a 1.[36] These may be attributed to the homology observed between certain allergens of ragweed (*Ambrosia*) and mugwort (*Artemisia*). The ragweed allergens Amb a 1, Amb a 4, Amb a 8 and Amb a 9, respectively, share homology with the mugwort allergens Art v 6, Art v 1, Art v 4 and Art v 5.[35,37–40] Among these, the high homology and cross-reactivity of the major allergens Amb a 1 and Art v 6 are key factors contributing to ragweed pollen allergy in regions with high concentrations of mugwort pollen. Studies have shown that compared with Art v 6, Amb a 1 contains more IgE epitopes and can elicit a more diverse range of allergen-specific IgE and T-cell responses in patients with weed allergies, playing a leading role in cross-reactions among homologous allergens.[41] However, in regions characterized by significant exposure to mugwort pollen, Art v 6 can act as the primary sensitizer, promoting sensitization to Amb a 1 through cross-recognition of T-cell and B-cell epitopes.[41,42]

Overall, in Asia, ragweed is not the primary pollen allergen, and sensitization rates are generally lower than those in North America and Europe. In China, ragweed is mainly distributed in northern regions, with sensitization rates among allergic populations ranging from 3.7 to 14.8%.[25,26] In Korea, rates among individuals with respiratory allergies range from 1.4 to 7.9%,[43,44] with a general population sensitization rate of 8.7% according to the 2019 Korea National Health and Nutrition Examination Survey.[11] Among allergic children in Japan, over 30% are sensitized to ragweed.[45]

When comparing ragweed allergy rates across different countries or regions globally, it is essential to consider the methodological differences in allergen detection and the impact of regional biases on result reliability. Although skin prick tests (SPT) and sIgE tests are often considered equivalent, significant differences between these methods can lead to inaccuracies in allergy rate comparisons. SPT exhibits high sensitivity but lower specificity, making it susceptible to factors such as operational techniques, allergen extract standardization (eg batch variations and concentration labeling), and patient medication (eg antihistamines), which can result in false negatives or positives. While sIgE offers higher accuracy, there are notable variations in sensitivity and specificity among different detection systems (eg FEIA, CLIA, ELISA). Additionally, the sources of allergen extracts (crude extracts vs recombinant proteins) and embedding techniques used by various reagent manufacturers can further contribute to inconsistent results. The lack of standardized detection protocols and threshold values across countries and institutions exacerbates inconsistencies in test outcomes. For instance, criteria for interpreting SPT wheal sizes (eg one-third of the positive control or absolute diameter) and the adoption of sIgE positivity thresholds (eg 0.35 kUA/L) vary, affecting the consistency of positive rate statistics. Ragweed pollen cross-reacts with other *Compositae* plants (such as mugwort and sunflower), and CCDs can cause false-positive results in detection.

Regional biases also influence allergy test results. The geographical distribution of ragweed directly affects its detection frequency as a major allergen. In areas where ragweed is not a primary allergen, low detection frequencies may lead to data gaps or underestimation. For example, in southern China, dust mite allergies dominate, and ragweed may not be included in routine testing panels, leading to potential result deviations. Conversely, in northern China, where ragweed is more prevalent and genetic susceptibility is higher, allergy rates are elevated, but reliance on SPT may introduce operational variability. In contrast, North America and Europe generally report higher ragweed allergy

rates, using more standardized sIgE tests (eg ImmunoCAP), enhancing data comparability. Moreover, in some Asian regions, such as northern China, cross-reactivity between mugwort and ragweed may overestimate ragweed allergy prevalence.

Ragweed Pollen Allergens

Ragweed is a wind-pollinated species that produces millions of tiny pollen grains per plant, each containing small air compartments located between the layers of the outer pollen wall. This unique structure facilitates the spread of ragweed pollen.[1] Ragweed pollen is a major source of airborne allergens, with most allergens originating from *A. artemisiifolia*, and a smaller amount from *A. trifida* and *A. psilostachya*. According to the official database of the International Union of Immunological Societies (IUIS database, https://www.allergen.org/), 11 allergens are identified from *A. artemisiifolia*, three from *A. trifida*, and one from *A. psilostachya* (Table 2).

Major Allergens

More than 90% of people with ragweed allergies are sensitized to Amb a 1, while 65% of these individuals also react to Amb a 11.[46,47] Around 40% of those with ragweed allergies are sensitized only to Amb a 1, approximately 30% to both Amb a 1 and 11, and about 15% predominantly to Amb a 11.[48] Notably, sensitization to Amb a 11 has been linked to more severe asthma symptoms.[49]

Table 2 Ragweed Allergens Recorded in the WHO/IUIS Database

Ambrosia		Allergen	Protein Family	Molecular Weight (kDa)	IgE Sensitization Rate
Ambrosia artemisiifolia **(Short ragweed)**	Major allergen	Amb a 1	Pectate lyase	38	90–95%
		Amb a 11	Cysteine protease	37 (natural purified mature protein), 52 (natural purified zymogen)	50–66%
	Minor allergen	Amb a 2	Renamed to Amb a 1.05		
		Amb a 3	Plastocyanine	11	30–50%
		Amb a 4	Defensin-like protein linked to polyproline-rich region	28–30	20–40%
		Amb a 5	Unknown	5	10–15%
		Amb a 6	Non-specific lipid transfer protein type 1	10	20–35%
		Amb a 7	Plastocyanin	12	15–20%
		Amb a 8	Profilin	14	20–35%
		Amb a 9	Polcalcin	9	10–15%
		Amb a 10	Polcalcin-like protein (4 EF-hands)	17	10–15%
		Amb a 12	Enolase	48	41–68%
Ambrosia psilostachya **(Western ragweed)**		Amb p 5	Unknown	5	Unknown
Ambrosia trifida **(Giant ragweed)**		Amb t 5	Unknown	5	5%
		Amb t 8	Profilin	14	50%
		Amb t 13	Superoxide dismutase	17	<5%

Amb a 1 is an acidic, non-glycosylated protein in the pectate lyase family, consisting of 397 amino acids (AA) and a molecular weight of approximately 38 kDa. Structurally, Amb a 1 has a core parallel beta-helix. During purification, natural Amb a 1 undergoes proteolysis, resulting in two noncovalently linked subchains: a 26 kDa alpha subchain (AA 181–396) and a 12 kDa beta subchain (AA 26–180). These subchains display distinct immunological properties, with Amb a 1α having lower IgE reactivity than Amb a 1β, which contains important IgE epitopes.[50] Amb a 1 includes five isoforms, with amino acid sequence identities ranging from 63 to 87%, each exhibiting varying IgE reactivity. In mouse models, the Amb a 1.01 isoform has shown higher IgE reactivity and has induced greater IgG and IgE antibody responses compared to the Amb a 1.02 and 03 isoforms.[51]

Amb a 11, another major allergen, belongs to the cysteine protease family and has a sensitization prevalence of up to 68.67%.[49] It is a glycosylated protein of 28 kDa with 262 amino acids. The crystal structure of pro-Amb a 11 resembles that of C1A cysteine proteases, with activity specifically inhibited by an N-terminal propeptide, which consists of five α-helices and lies adjacent to the mature domain composed of six α-helices and a β-sheet.[52] Currently, only one isoform of Amb a 11 is registered in the IUIS database, though mass spectrometry suggests that natural Amb a 11 may have at least 20 isoforms and glycoforms.[48]

Minor Allergens

Amb a 8, a 133-AA prolifin, has a molecular weight of 14 kDa and a sensitization rate between 20 and 35%.[46] Structurally, it contains two terminal α-helices, one short α-helix, and a β-hairpin surrounding a central five-stranded antiparallel β-sheet.[53]

Amb a 9 and Amb a 10 are polcalcins within the calcium-binding protein family, sensitizing about 10–15% of ragweed-allergic individuals. Amb a 9 has a molecular weight of 9 kDa with 82 AA and contains two EF-hand domains, while Amb a 10, weighing 18 kDa with 160 AA, has three EF-hand domains.[37] Profilins, calcium-binding proteins (CBPs), and non-specific lipid transfer proteins (nsLTPs) act as pan-allergens, often contributing to broad cross-sensitization in pollen allergy patients.[33]

Given the high conservation of amino acid sequences in the profilin family, most patients sensitized to Amb a 8 also exhibit cross-sensitization to profilins such as Art v 4 (mugwort), Hel a 2 (sunflower), Bet v 2 (birch), and Phl p 12 (timothy grass), sharing 89, 81, 74, and 79% sequence identity, respectively.[37,53] In a recent study, 91% of patients with rAmb a 8-positive sera reacted to rBet v 2, while all rAmb a 8-positive patients also showed IgE reactivity to rArt v 4 and rPhl p 12.[38]

Amb a 9 and Amb a 10 share sequence homology with other calcium-binding proteins across different sources. Amb a 9, for example, shares 82, 71, 71, and 68% sequence identity with Art v 5 (mugwort), Bet v 4 (birch), Ole e 3 (olive), and Aln g 4 (alder), respectively. Amb a 10 has the highest sequence similarity with Ole e 8 (olive) and Jun o 4 (juniper).[37]

Amb a 6 is a 10 kDa, type I nsLTP protein with a predominantly α-helical secondary structure,[54] sensitizing approximately 21% of ragweed-sensitive individuals.[55] Amb a 6 is distinct from other nsLTP allergens in that it does not show IgE cross-reactivity, likely due to low sequence similarity with other nsLTPs; notably, it is not linked to nsLTP-induced plant food allergies.[54]

Amb a 3, a glycoprotein in the plastocyanin family, is 101 amino acids long with a molecular weight of 11 kDa, sensitizing 30–50% of those with ragweed allergies. Another minor allergen, Amb a 7, also from the plastocyanin family, has a molecular weight of 12 kDa and a sensitization rate between 15 and 20%.

Amb a 4, a 30 kDa glycoprotein in the defensin-like family, has a sensitization rate between 20 and 40%. Amb a 4 belongs to the defensin-polyproline-linked protein group specific to Asteraceae pollen, sharing structural homology with defensin-like allergens such as Art v 1 and Par h 1. This allergen family typically exhibits O-linked glycosylation on hydroxyproline residues.[39]

Amb a 5 is a smaller allergen of 5 kDa and 45 AA, recognized by serum IgE in 10–15% of ragweed-sensitive individuals.

Amb a 12, a phosphopyruvate hydratase (enolase) with a molecular weight of 48 kDa, has a sensitization prevalence of 41–68%. It shows high sequence similarity, up to 90%, with Hev b 9 from the rubber tree (*Hevea brasiliensis*), and at

least 60% identity with enolases from other sensitizing sources, suggesting potential cross-reactivity with other common pollen and food allergens.[56]

Component-Resolved Diagnostics

The SPT and serum sIgE tests are widely used for diagnosing allergies; however, they often struggle to distinguish between true sensitization and cross-reactivity. CRD allows for IgE sensitization testing across various allergens, providing enhanced specificity in diagnosing cross-reactivity and co-sensitization, which is especially important for polysensitized patients[57] and enables a tailored approach to AIT. Research has shown that CRD influences allergen selection in AIT in over 50% of cases.[58] Cost has shown to be a major barrier to widespread CRD use. Currently, only natural or recombinant Amb a 1 and 4 are available for singleplex or multiplex CRD systems.[59–61]

It is worth noting that Amb a 4 and Art v 1 are homologous, defensin-like proteins, exhibiting high similarity and cross-reactivity.[62] Similarly, the major allergen Amb a 1 and its homolog Art v 6, both from the pectin lyase allergen family, also show cross-reactivity.[40] Thus, CRD testing for Amb a 1 and Amb a 4, or for Art v 1 and Art v 6, enables accurate differentiation between true sensitization to ragweed and mugwort pollen.[38]

Treatment Strategies for Ragweed Allergy

Ragweed pollinosis is one of the most prevalent seasonal allergies, affecting approximately 30% of the global population.[63] Among more than 50 *Ambrosia* species, short ragweed is the most widespread, frequently triggering hay fever during late summer and autumn, especially in North America and Europe. Exposure to ragweed pollen often leads to type I hypersensitivity reactions, causing symptoms such as seasonal allergic rhinitis, conjunctivitis, asthma, and, in some cases, skin reactions.

Managing ragweed allergy involves allergen avoidance, pharmacotherapy, and AIT. Reducing allergen exposure can significantly lessen symptoms, with strategies like wearing masks and limiting outdoor activities during peak pollen season. Additionally, keeping windows closed and using air conditioning during the day can help minimize indoor pollen levels. However, complete avoidance is challenging; thus, controlling the spread and growth of ragweed remains essential in managing exposure.

Treatments for Ragweed-Induced Allergic Rhinitis

Seasonal allergic rhinitis is on the rise, potentially due to longer pollen seasons and higher pollen concentrations associated with climate change.[64] Ragweed-induced allergic rhinitis typically presents with sneezing, runny nose, itching, and nasal congestion, with symptom severity often correlating with environmental pollen levels. These symptoms generally improve once exposure ends or treatment begins.[65]

Pharmacotherapy for seasonal allergic rhinitis typically includes oral second-generation antihistamines, intranasal antihistamines, intranasal corticosteroids (INCS), leukotriene receptor antagonists (LTRAs), intranasal decongestants, and intranasal mast cell stabilizers.

Oral second-generation antihistamines (eg fexofenadine, cetirizine, levocetirizine, desloratadine) are the recommended first-line treatment for ragweed-induced AR, as they have fewer central nervous system and anticholinergic side effects than first-generation options. Intranasal antihistamines, such as azelastine or olopatadine, can serve as first- or second-line treatments, offering rapid symptom relief, particularly for nasal congestion, and outperforming INCS in managing ocular symptoms.[66,67]

INCS (eg fluticasone, triamcinolone, budesonide, mometasone) are also considered first-line treatments due to their effectiveness in controlling nasal symptoms. Ideally, patients start using INCS before the onset of pollen season, though long-term use should be limited due to potential side effects such as epistaxis.[68]

LTRAs, though not first-line options, are approved by the US Food and Drug Administration (FDA) for seasonal AR in patients aged two and older; however, they are generally less effective than antihistamines and INCS,[69,70] and they come with an FDA boxed warning for potential neuropsychiatric side effects. Additionally, the initial preference did not involve the utilization of alternative therapeutic agents such as intranasal decongestants (oxymetazoline) and intranasal mast cell stabilizers (cromolyn sodium).

Emerging therapies include barrier agents, Anti-H3 and Anti-H4 antihistamines, selective CRTH2 antagonists, and biologics. While these treatments show promise, more research is needed to confirm their safety and effectiveness. Barrier agents like nonpharmacological intranasal cellulose powder, lipid microemulsions, and xyloglucan spray create a protective layer over nasal mucosa to prevent direct contact.[71] Fexofenadine combined with an H3 receptor antagonist (PF-03654746) has shown moderate symptom relief, though it is less effective than combining fexofenadine with pseudoephedrine.[72,73] Selective H4 receptor antagonists are still being studied but show anti-inflammatory effects in animal models.[74]

Selective CRTH2 antagonists have shown positive results in relieving AR and asthma symptoms in clinical trials. The dual antagonist Ramatroban, which targets CRTH2 and TP receptors, is already approved for allergic rhinitis in Japan.[75] Biologic agents like omalizumab, mepolizumab, dupilumab, benralizumab, and ranibizumab have the potential for symptom relief, although they currently lack approval for AR. Omalizumab combined with ragweed immunotherapy has shown significant improvement over immunotherapy alone and can also help reduce adverse reactions in accelerated immunotherapy regimens for ragweed allergic rhinitis.[76,77]

Treatments for Ragweed-Induced Allergic Asthma

Ragweed pollen has been found to trigger asthma at double the rate compared to pollen types.[78] Individuals sensitized to ragweed may experience asthma-related symptoms such as wheezing, coughing, and dyspnea, often characterized by reversible airflow obstruction and increased airway hyperresponsiveness.

Inhaled corticosteroids (ICS) are the primary anti-inflammatory treatment for maintaining control of allergic asthma. However, prolonged use of ICS can increase the risk of side effects, particularly in pediatric and elderly patients. For those with seasonal allergic asthma who only experience symptoms during the ragweed pollen season, it is recommended to start daily ICS treatment or use a low-dose ICS-formoterol combination as needed. This treatment should continue for four weeks after the end of the ragweed pollen season to ensure symptom control.[79] LTRAs are an alternative for patients with mild asthma, though they are less effective than ICS when used alone.

Short-acting beta$_2$ agonists (SABA) are no longer employed for monotherapy. Any use of SABA should be combined with a low-dose ICS, typically through an ICS-SABA combination inhaler. A more effective long-term treatment involves combining ICS with long-acting beta$_2$ agonists (LABA), which provide bronchodilator and anti-inflammatory effects. This combination therapy helps manage asthma symptoms and reduces the likelihood of acute exacerbations.[79]

Biologic therapies are considered for patients who do not achieve adequate asthma control or experience frequent acute exacerbations despite optimal treatment with medium to high doses of ICS and LABA. Six biologics are FDA-approved for asthma management: omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab. These biologics are highly effective in reducing severe asthma exacerbations, improving forced expiratory volume in one second (FEV1), enhancing quality of life, and improving overall asthma management. Additionally, benralizumab, dupilumab, and mepolizumab have been shown to decrease the need for daily oral corticosteroids (OCS).[80] However, there is limited clinical evidence on the specific use of these biologics for ragweed-induced allergic asthma.

Treatments for Ragweed-Induced Allergic Conjunctivitis

Ragweed pollen is a common trigger for seasonal allergic conjunctivitis (SAC), which is characterized by symptoms such as itchy eyes, pain, redness, periocular swelling, and tearing. SAC often coexists with allergic rhinitis or other allergy-related conditions.

Treatment for SAC includes various pharmacologic options: topical vasoconstrictors, mast cell stabilizers, antihistamines, and dual-action agents that offer both mast cell stabilization and antihistamine effects, as well as topical corticosteroids and immunomodulating agents like cyclosporine and tacrolimus. Oral and topical antihistamines are the mainstay treatments for allergic conjunctivitis, with dual-action agents—such as azelastine, epinastine, alcaftadine, bepotastine, ketotifen, and olopatadine—being the most used due to their combined mast cell-stabilizing and antihistaminic properties. Topical corticosteroids or allergen immunotherapy is typically reserved for severe cases.[81]

Additionally, non-pharmacological approaches like cold compresses can reduce ocular edema and redness, while artificial tears or ocular surface lubricants help dilute and remove allergens from the ocular surface, relieving symptoms.[82]

Allergen Immunotherapy for Ragweed

AIT is recommended for patients with ragweed-induced AR, rhinoconjunctivitis, or allergic asthma who do not achieve adequate symptom relief from optimized medical therapy and environmental exposure reduction. Unlike other treatments, AIT not only alleviates symptoms but also modifies the disease's progression by inducing immune tolerance, making it the only treatment with the potential for long-term improvement. Both SCIT and SLIT using ragweed extracts have shown sustained clinical benefits, even following the conclusion of therapy. Additionally, AIT is generally safe with minimal side effects and provides a more cost-effective option than prolonged pharmacotherapy.

The main component in ragweed allergy immunotherapy extracts is Amb a 1, a major allergen in ragweed pollen that has a sensitization rate of over 90%. Standardized allergen extracts are recommended to ensure consistent biological activity, and in the United States, ragweed extracts are normalized for Amb a 1 content. For maintenance SCIT, a dose of 6–12 μg Amb a 1 is advised per injection. Cross-reactivity among various ragweed species[83] and extracts from *A. artemisiifolia* effectively inhibit IgE reactivity to other ragweed species like Amb p (*Ambrosia psilostachya*) and Amb t (*Ambrosia trifida*) by over 90%. As a result, immunotherapy targeting Amb a may offer benefits for patients exposed to multiple ragweed species.[84]

After SCIT treatment, patients with seasonal rhinoconjunctivitis and/or asthma exclusively sensitized to short ragweed showed substantial reductions in rhinoconjunctivitis, asthma, and medication scores at one- to two-year follow-up.[85]

SLIT is commonly available in liquid or tablet form. In 2014, the FDA approved a sublingual ragweed tablet (MK-3641) specifically for adults with ragweed-induced AR. It is recommended to start treatment at least 12 weeks before the beginning of the ragweed pollen season, with the 12 μg Amb a 1 SLIT tablet recognized as a safe and effective option.[86]

Studies in Europe and North America demonstrate a dose-dependent effect of the sublingual ragweed tablet (MK-3641) in adults with AR, with or without conjunctivitis (AR/C). Daily AIT doses of 12 μg Amb a 1 significantly reduce the total combined score (TSC), daily symptom score (DSS), and daily medication score (DMS).[87–89] In children with ragweed pollen-induced AR/C, ragweed SLIT tablets show marked improvement in symptoms and reduce the need for relief medications. Additionally, SLIT tablets have proven effective in alleviating asthma DSS, lowering SABA use, and reducing nocturnal awakenings in children with asthma. According to the 2024 Global Initiative for Asthma (GINA), SLIT therapy may be considered as an adjunct treatment for asthmatic children allergic to ragweed during pollen season, provided their FEV1 is ≥80% of the predicted value.[79,90]

Ragweed SLIT has shown good tolerability in both European and North American populations, with no serious or life-threatening incidents. The most common treatment-related adverse events (TRAEs) are typically manifested early in the course of therapy and are self-limiting. These events are generally classified as mild to moderate, occurring mainly as localized reactions, such as oral pruritus, throat irritation, tongue edema, and auricular pruritus.[91] The SLIT tablet for ragweed is similarly well tolerated in children, showing a comparable adverse event (AE) profile to adults.[90]

Biological Control of Ragweed

Beyond conventional methods like mowing, low-impact herbicides, hardscaping, and planting competitive vegetation, classical biological control is regarded as the most effective strategy for managing ragweed.[6,92] Biological control is a strategic approach that intentionally leverages the natural enemies of weeds to reduce their population density. While this approach does not fully eradicate the target weed, it applies sufficient pressure to lower its dominance to a more manageable level. Biological control is also cost-effective, environmentally friendly, self-sustaining, and aligns well with integrated weed management.[93]

The case of *Ophraella communa* and *Epiblema strenuana*, which are both native North American species with high host specificity, has shown strong potential as potential control agents.[94,95] *Ophraella communa* and *Epiblema strenuana*

exert effective control over the proliferation and dissemination of ragweed through direct herbivory on its leaves and stems, thereby diminishing its reproductive potential and constraining its growth and spread. *O. communa* has a significant inhibitory effect on the growth of ragweed, particularly by inflicting substantial damage to its reproductive structures during the late growing season, which may affect the pollen release and allergenic potential of ragweed.[96] *O. communa* has high specificity towards ragweed and has minimal impact on other plant species, suggesting that its use as a biological control agent poses a low risk.[97,98] *Epiblema strenuana* effectively controls the growth and spread of *Ambrosia artemisiifolia* through its specific parasitism, destruction of the plant's vascular tissues, high reproductive potential, strong dispersal ability, and synergistic interactions with other natural enemies.[94,99]

A study in Europe found that the leaf beetle *O. communa* significantly reduced ragweed pollen concentrations, leading to fewer allergy cases and healthcare costs.[6] In southern China, both species have effectively controlled ragweed spread; however, their impact has been less pronounced in northern regions.[94,100,101] A recent study analyzing the ecological niche separation and overlap between the two natural enemies predicts that their efficiency in controlling ragweed in northern and northeastern China will increase under projected climate conditions for the 2030s and 2050s.[100]

Conclusion

Ragweed pollen is a prevalent allergen in North America and Europe, and its spread to other regions, including Asia, calls for serious attention to the allergies it induces—such as allergic rhinitis, conjunctivitis, and asthma. Significant progress in specific AIT for ragweed has been made in recent years, with SLIT tablets offering a more convenient alternative to SCIT, thereby overcoming certain usage limitations and improving patient adherence. However, current AIT formulations for ragweed largely focus on Amb a 1, with limited research on AIT targeting other allergenic components. Advances in CRD technology may enable personalized AIT tailored to individual allergen components in the future. As ragweed allergy becomes an increasingly global health issue, a comprehensive approach involving allergen identification, treatment optimization, and biological weed control is essential.

Abbreviations

AIT, allergen immunotherapy; CRD, Component-resolved diagnosis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; sIgE, specific immunoglobulin E; AR, allergic rhinitis; CCDs, cross-reactive carbohydrate determinants; AA, amino acids; CBPs, calcium-binding proteins; nsLTPs, non-specific lipid transfer proteins; SPT, skin prick test; INCS, intranasal corticosteroids; LTRAs, leukotriene receptor antagonists; ICS, Inhaled corticosteroids; SABA, Short-acting beta$_2$ agonists; LABA, long-acting beta2 agonists; FEV1, forced expiratory volume in one second; OCS, oral corticosteroids; SAC, seasonal allergic conjunctivitis; TSC, total combined score; DSS, daily symptom score; and DMS, daily medication score; TRAEs, treatment-related adverse events; AE, adverse event.

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