

New and old adjuvants in allergen-specific immunotherapy: With a focus on nanoparticles

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Abstract

Allergic diseases have remarkably increased in recent years. Nowadays, efforts for curing and management of these disorders are an important concern worldwide. Allergen-specific immunotherapy (ASIT) has recently gained more attention as a means for the management of allergic diseases. Adjuvants or helper agents are materials applied for better stimulating and shifting of protective responses, and these belong to an extremely diverse collection of complexes. The main function of adjuvants includes acting as depot foundations, transferring vehicles, and immunostimulators. Immunostimulatory adjuvants have gained increasing attention for ASIT. In this regard, the present study provides a review of old and new adjuvants used in allergen immunotherapy.

KEYWORDS

adjuvants, allergen-specific immunotherapy, allergies, immunotherapy, nanoparticles

1 | INTRODUCTION

According to numerous epidemiological studies, the frequency of immunoglobulin E (IgE)-mediated allergic disorders has noticeably increased in recent years and affected about 30–40% of the population, mostly in developed countries (Bousquet, Van Cauwenberge, & Khaltaev, 2001; Traidl-Hoffmann et al., 2003). The medical symptoms of IgE-mediated hypersensitivity reactions consist of a number of limited and systemic lethal reactions (C. A. Akdis & Akdis, 2015). Allergy, as a pathological state, refers to an uncommon fast response to several innocuous ecological mixtures, that is, allergens from diverse sources (e.g., pollen, dust; Venarske & deShazo, 2003). These diseases are characterized by an increase in CD4⁺ TH2 cells, type-2 cytokine, and IgE antibodies, and, lastly, the recruiting of effector cells of the immune system (Hamilton, MacGlashan, & Saini, 2010; Rindsjö & Scheynius, 2010). The etiology of allergic disorders (food allergy, asthma) is multifarious; it seems that complex interactions between internal and external factors are associated with the amplified incidence of such disorders during the last decade (Jenerowicz et al., 2012). To describe allergies, a number of exploratory and experimental studies have been carried out to treat and control these diseases (Novak, 2009; Rolland, Gardner, & O'hehir, 2009). Controlling

IgE-mediated allergic diseases involves avoiding allergens through medications and allergen-specific immunotherapy (ASIT) (Pfaar et al., 2014). Pharmacotherapies based on taking antihistamines, steroids, and immunosuppressive drugs on a regular basis can efficiently decrease symptoms of allergic diseases, and improve quality of life (Jutel, 2014). At present, SIT for allergic patients can be considered as the singular management method for altering pathological circumstances into a normal immune response (Di Lorenzo, Leto-Barone, La Piana, & Di Bona, 2017). In immunotherapy, in contrast to traditional vaccination, desensitization of patients is done via a systemic inoculation via incremental doses of the allergen over an extended time period (M. Akdis, 2017; Rajakulendran, Tham, Soh, & Van Bever, 2018). ASIT shifts immune response to allergens from the TH2-type response to a TH1-type immune response (M. Akdis & Akdis, 2007). Given the limitations of the immunotherapy technique, building safe and effective vaccines requires harmless and efficient adjuvants (M. Akdis & Akdis, 2014). Adjuvants in conventional immunotherapy help the immune response to the inoculated allergen (Francis & Durham, 2004). Considering the unique features of nanoparticle-based allergen-delivery systems, using nanoparticles (NPs) as new adjuvant agents has improved the potential of successful ASIT (Pandey et al., 2011). Therefore, in this study, we will discuss old and new adjuvants used in ASIT.

2 | CHARACTERISTICS OF ALLERGIC IMMUNE DISORDERS

The development of allergic disorders is characterized by a difference in the ratio of the Th1 and Th2 CD4⁺ cells and the T regulatory (T_{reg}) cells (M. Akdis & Akdis, 2007). This disease occurs in two stages: sensitization and expansion of memory T and B-cell responses and IgE (initial stage), and the effector functions connected to tissue infection and damage (second stage; C. A. Akdis & Akdis, 2011). Th2 CD4⁺ cells are the chief agent in the allergic response (Galli, Tsai, & Piliponsky, 2008). The sensitization stage happens after the initial contact with a particular allergen. The allergen is taken by antigen-presenting cells (APCs) that present antigenic peptides to naive CD4⁺ T cells, activating a Th2 cell response. Then, CD4⁺ Th2 cells prompt class changing in B cells to produce IgE specific for the allergen (C. A. Akdis & Akdis, 2011). These specific antibodies connect to the IgE antibody receptors on effector cells, which express on membranes of circulating mast cells and basophils that exist in the skin and mucous membranes (C. A. Akdis & Akdis, 2011, 2015). When the next contact with the allergen occurs, the allergen cross-connects with two molecules of mast cell-bound IgE, stimulating an instant hypersensitivity response (Calderon et al., 2011). This signal results in basophil and mast cell degranulation and the discharge of diverse symptoms of the allergic disease (Frew, 2010; Kündig & Bachmann, 2010; Figure 1).

3 | ALLERGEN-SPECIFIC IMMUNOTHERAPY

Currently, hyposensitization or Immunotherapy is the widely accepted and unique, effective, and specific therapy for IgE-mediated allergic diseases that is capable of altering the normal immune response to ameliorate the symptoms (C. A. Akdis & Akdis, 2015). SIT involves recurrent administrations of minor but regularly increasing quantities of disease-inducing allergen(s) along with an adjuvant (Eggleston, 1997). The SIT mechanisms have a unique ability to shift

the inappropriate specific immune responses from the Th2-dominated, mainly IgE production pattern to a diverse defending Th1/Treg cell (Treg) form, resulting in the suppression of antibodies and improvement of peripheral tolerance (M. Akdis, 2017; Ye, Chuang, & Chiang, 2011). Nevertheless, despite the efficacy of SIT, some limitations of this treatment result in severe IgE-mediated side effects such as difficulties in the standardization of allergen extracts, common allergen injections, adverse reaction to allergen administration, high cost, extensive treatment duration, adjuvant type, application route and safety issues, and inadequate efficacy (Sakaguchi, Hirahara, Fujimura, & Toda, 2011). Therefore, there is an urgent need for new healing plans for treating IgE-mediated conditions, and these can be achieved by applying changes in SIT, such as reducing the number of injections, finding suitable adjuvants to reduce the administered allergen dose to encourage suitable immune response, potentially improving patient compliance and value of life, while reducing healthcare problems (Frew, 2010; Novak, Bieber, & Allam, 2011).

3.1 | Protocols of ASIT

Despite the efficacy of ASIT, its basic mechanisms are not fully understood (M. Akdis & Akdis, 2014). Cellular and molecular actions that happen during ASIT for the immune-tolerant state contain the initial desensitization effects, and the production of Treg and Breg cell responses, mainly, in the allergen-specific effector T-cell subclasses and connected antibody classes (C. A. Akdis & Akdis, 2011). The enlarged levels of transforming growth factor- β and interleukin (IL)-10 produced by Treg cells can strongly overwhelm IgE generation, modulating class creation with high production of IgG antibodies, such as allergen-specific IgG1 and IgG4 that have obstructive and anti-inflammatory action (M. Akdis & Akdis, 2014). Then again, the amount of Th2 cells, and the amounts and actions of mast cells and eosinophils in allergen description sites have occurred (C. A. Akdis & Akdis, 2009; Ciprandi, Marseglia, & Tosca, 2016).

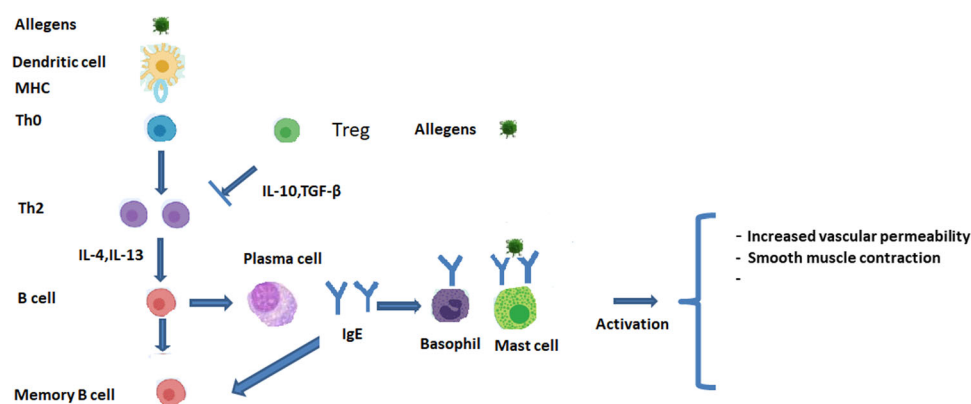


FIGURE 1 Mechanisms of allergic diseases. An allergic disease occurs through allergen recognition from different sources and finally results in a number of biological effects such as increased vascular permeability. IgE, immunoglobulin E; IL, interleukin; MHC, major histocompatibility complex; TGF- β , transforming growth factor- β

Furthermore, SIT results in Treg cells-activating peripheral T-cell tolerance by overpowering dendritic cells (DCs) that handle the production of effector T cells (Ciprandi et al., 2016). After SIT, a rise in Th1/Th0 and CD8+ cells and a decrease in Th2/Th0 proportion are discovered (Compalati, Braidó, & Canonica, 2013). Moreover, since it alters cytokine response with IL-5 and IL-4 production reductions (Th2), interferon (IFN)- γ production rises (Th1; M. Akdis & Akdis, 2014). Today, two types of AIT are in clinical practice, that is, sublingual immunotherapy and subcutaneous immunotherapy. However, the traditional technique of administering SIT is through the subcutaneous injection route (SCIT; Frew, 2010). Efforts for safer and more appropriate and useful plans for stunned SCIT restrictions are in exploration, which includes the production of recombinant allergens, novel adjuvants preferring particular TH1 responses, as well as diverse ways of administering SIT, particularly through the sublingual delivery of the allergen (Bauer & Rank, 2014; Canonica & Compalati, 2015).

4 | ADJUVANTS FOR ALLERGEN IMMUNOTHERAPY

The general aim of allergen vaccine development is to improve medical safety and efficacy (Moingeon, 2012). Currently, a unique approach for developing vaccines for SIT is to utilize routine adjuvants that selectively control the immune response to provoke specific immune responses (Aguilar & Rodriguez, 2007). Most protein antigens and allergens are required to be delivered by an adjuvant to guarantee a better immune response with long-term effects (Schöll, Boltz-Nitulescu, & Jensen-Jarolim, 2005). The term adjuvant refers to any "substance" that can act nonspecifically to increase the immunogenic strength of the associated antigen or/and increase the specific immune response to an antigen (Kool & Lambrecht, 2014; Wang & Singh, 2011). An extensive set of diverse adjuvants are used in immunization protocols, and the selection is mainly based on the desired response (De Souza Rebouças et al., 2012). The main considerations for using specific adjuvants include an equilibrium between trying to achieve a high grade of directed immune responsiveness and minimizing opposing nonspecific inflammatory outcomes (Schunk & Macallum, 2005). These adjuvants, together with the immunostimulatory outcome, should not cause autoimmunity, mutagenicity, and oncogenicity, and must be nonfebrile and stable in the vaccine formulation (Francis & Durham, 2004). Despite the benefits of adjuvants for routine vaccines, we need to focus on the major side effects and harmfulness of these agents (Aguilar & Rodriguez, 2007; Gamazo, Gastaminza, Ferrer, Sanz, & Irache, 2014). Adjuvants are conventionally put in allergy vaccines to permit simplifying immunization schedules; induce primary, significant, and lifelong immune response; and achieve efficacy faster and for a longer period (N. K. Gupta, Tomar, Sharma, & Dixit, 2011; Moingeon, 2012). Ideally, an adjuvant would have a satisfactory safety pattern, and would offer improved immunogenicity for vaccines to allow lesser doses of an allergen to be delivered (Gamazo

et al., 2014). Notably, because allergy vaccines are therapeutic vaccines, using appropriate adjuvants for allergy immunotherapy in patients should shift the immune response to Th1 or Treg cells, both known to downregulate Th2 cells (Moote, 2011). Numerous novel adjuvants for allergen immunotherapy with a focus on nanoparticle vector system are presently being inspected and advanced in preclinical models or in humans (Table 1 and Table 2).

4.1 | Mechanisms of action

Adjuvants belong to an extremely diverse collection of chemically complex materials (Perrie, Mohammed, Kirby, McNeil, & Bramwell, 2008). These materials can be categorized into different substances with respect to their means of adjuvanticity action according to their mechanisms (Cox, Verdonck, Vanrompay, & Goddeeris, 2006; Moingeon, 2012). Usually, adjuvants are classified into four groups: Group (I) initiating depot foundation at the location of inoculation (for instance, oil-based adjuvants, mineral compounds, biodegradable polymer microspheres), and Group (II) acting as transferring vehicles for the antigens (e.g., oil adjuvants, nonionic block polymer surfactants, liposomes, biodegradable polymer microspheres). In addition, adjuvants in Group (III) act as immunostimulators (e.g., muramyl dipeptide (MOP), monophosphoryl lipid A [MPL], Freund's complete adjuvant, lipopolysaccharide, cytokines, and lipid A; de Souza Apostólico, Lunardelli, Coirada, Boscardin, & Rosa, 2016). Immunostimulatory (Immunopotentiator) adjuvants, which increase the immunogenicity of specific allergens, while not being pharmacologically active themselves, have been used for many years in SIT vaccines (Reisacher & Schwanke, 2016). However, some compounds can act by more than one mechanism concurrently (Aguilar & Rodriguez, 2007; Perrie et al., 2008). Adjuvants can be used for numerous purposes: (a) development of the immunogenicity of antigens; (b) decreasing the volume of antigen or amount of immunizations required; (c) increasing the antigen attendance; (d) improving antigen acceptance to APCs; (e) prompting the making of immunomodulatory cytokines; and (f) acting as antigen transfer systems (Gamazo et al., 2014; Figure 2).

4.1.1 | Mineral adjuvant

These immunopotentiators adjuvants, such as calcium phosphate or aluminum hydroxide, are mostly used in humans as adjuvants for subcutaneous allergic vaccines. Aluminum salts are usually involved in vaccines against infectious pathogens with the aim of mitigating proinflammatory responses after the activation of the inflammasome (Wilcock, Francis, & Durham, 2004).

Aluminum hydroxide

The salts of aluminum that are used most commonly for vaccines such as antiallergies are aluminum potassium sulfate (alum), aluminum hydroxide, and aluminum phosphate (Wheeler &

TABLE 1 Animal studies of various adjuvants in allergic disorders

Model of study	Type of adjuvant	Influence on cytokine pattern or diseases (decrease or increase)	References
Mouse (sc)	CpG conjugated to cedar and grass pollen Phl p 5 allergen	• Reduce TH2 cytokines • Reduced eosinophil lung infiltration • Suppressed specific IgE and IgG1 • Increase of allergen-specific IgG2a • Increase IFN-γ by T h1cells	Hessenberger et al. (2013); Kaburaki et al. (2011)
Mouse	ISCOMS-OVA	• Generating a Th1 response • Only induce IgG	Maloy, Donachie, and Mowat (1995)
Mouse (ip injection)	Liposome—artemisia pollen allergens	• Longer time in the tissues in compared to free allergen	Arora and Gangal (1991)
Mouse	IMQs	• Decreased lung inflammation, and eosinophil infiltration in the airways • Rising in specific IgG2a • Reduce in specific IgE	Vultaggio et al. (2009)
Mouse	Proticles (protamine) combined with Ara h 2 extracted	• Downregulate Th2-dominated immune response	Pali-Schöll et al. (2013)
Mouse	Carbohydrate-based particles coupled to grass pollen antigen	• Th1 cytokine production was enhanced	Ulrich, Cieplak, Paczkowski, Taylor, and Sanderson (2000)
Mouse	PLGA—recombinant Bet v1 (the major allergen of birch pollen)	• Decrease the majority of the TH2 • Rising the IgG2a levels • Rise in IL-10 and IFN-γ levels	Schöll et al. (2004)
Mouse	PLGA—olive allergen	• Induced a Th1 response	Batanero, Barral, Villalba, and Rodríguez (2003)
Mouse	PLGA—loaded with ovalbumin	• Lower ranks of IgG1 • Higher ranks of IgG2a • Higher IL-10 levels and IFN-γ levels	Apicella et al. (2009)
Mouse	Gantrez AN nanoparticles loaded with ovalbumin	• Th1 and Th2 markers (IgG2a and IgG1, separately) were improved • Protection from anaphylactic shock	S. Gómez et al. (2007)
Mouse	Peanut proteins—poly(anhydride) NP	• Strong mixed TH1/TH2-type immune response was observed	Rebouças et al. (2012)
Mouse	Embarrass of Ags of Aspergillus fumigatus in PVP nanoparticles	• Continued IgG levels • IgE levels were lesser than detected in free allergens studies	Madan et al. (1997)
Mouse	Gene transport with chitosan—DNA nanoparticles orally	• Significant decrease of anaphylaxis, IgE level, vascular leakage, and plasma histamine	Roy, Mao, Huang, and Leong (1999)
Mouse	Der f 2—loaded chitosan microparticles	• Reduced airway hyperactivity • Reduced amounts of eosinophils in BAL fluid • Relieved lung inflammation • Decrease mucus creation • Decreased IgE in serum • Increased IgG2a in serum	Li, Liu, Wu, Wu, and Ran (2008)
Mouse	In vivo and in vitro using of AgNPs by model antigens OVA and BSA	• Reduced IgG production • Reduced Th2 immune responses • Rise of IgG1/IgG2a and IgE • Rise of peritoneal leukocytes I, TNF-α, and IFN-γ	Xu, Tang, Liu, Wang, and Liu (2013)

Abbreviations: BSA, bovine serum albumin; CpG, cytosine-phosphate-guanine; IFN- γ , interferon- γ ; Ig, immunoglobulin; IL, interleukin; IMQ, imidazoquinoline; ip, intraperitoneal; ISCOM, immune-stimulating complex; NP, nanoparticle; PLGA, poly(lactide-co-glycolic acids); PVP, poly(vinylpyrrolidone); sc, subcutaneous; TGF- β , transforming growth factor- β .

TABLE 2 Human studies of different adjuvant in allergic disorders

Model of study	Type of adjuvant	Effect on cytokine pattern or disorders (increase or decrease)	References
Human (ragweed allergy)	CpG motifs	• Amplified Th1 cytokines levels • Reduced Th2 cytokines levels	Simons, Shikishima, Van Nest, Eiden, and HayGlass (2004)
Human (randomized double-blind, placebo-controlled)	CpG motifs	• Amplified Th1 cytokines levels • Reduced Th2 cytokines levels • Reduction in specific seasonal-induced IgE	Creticos et al. (2006)
Human (Amb a 1) placebo-controlled clinical study	CpG motifs	• Reorientation of Th2 to Th1 responses • Amplified CXCL-10, CXCL-9, and INF-γ • Reduced CCL-22, CCL-17, and IL-5	Simons et al. (2004)
Human (Der p 1)	VLP-Der p 1	• Improvement of immunogenicity • Boost the effectiveness of allergen-specific immunotherapy	Kündig et al. (2006)
Human (sc in asthmatic patient)	Mite allergens- liposomes	• Fewer bronchial, nasal, and ocular symptoms • Decrease Th2 pattern • Increase Th1 pattern	Basomba et al. (2002)
Human (grass pollen extract)	MPL	• Enhanced IgG1 and IgG4 • Reduce the number of preseasonal injections	Mothes et al. (2003)
Human (double-blind placebo-controlled)	MPLA in conjunction with modified grass allergen	• Demonstrated a 24.3% and 48% improvement in symptoms during the four peak pollen weeks, respectively	Patel, Holdich, von Weikersthal-Drachenberg, and Huber (2014)

Abbreviations: CpG, cytosine-phosphate-guanine; INF- γ , interferon- γ ; IgG, immunoglobulin G; IL, interleukin; MPLA, monophosphoryl lipid A; sc, subcutaneous; VLP, virus-like particle.

Woroniecki, 2001). Aluminum hydroxide (alum) was initially known as an adjuvant over 70 years ago, and today they continue to be the most common for injections related to immunotherapy in human and veterinary vaccines (Brewer, 2006; Francis & Durham, 2004). The immunostimulating influence of the alum is ascribed to several various mechanisms (Lindblad, 2004). Alum adjusting antigen release for persistent antigen expression also stimulates high titred and long-lasting antibody responses in humans (Schöll et al., 2005). In general,

aluminum adjuvants have immunomodulatory properties and good safety patterns (Lindblad, 2004). Nowadays, the most commonly used adjuvants in human subjects for the SIT vaccines for type I allergy are aluminum-based, which induce a proallergic Th2-type response (Gamazo et al., 2014; Schöll et al., 2005). Despite extensive use of alum, they have a number of drawbacks (including harshness of confined tissue irritation, the extended period of the inflammatory reply at the inoculation place, and vigorous Th2 responses;

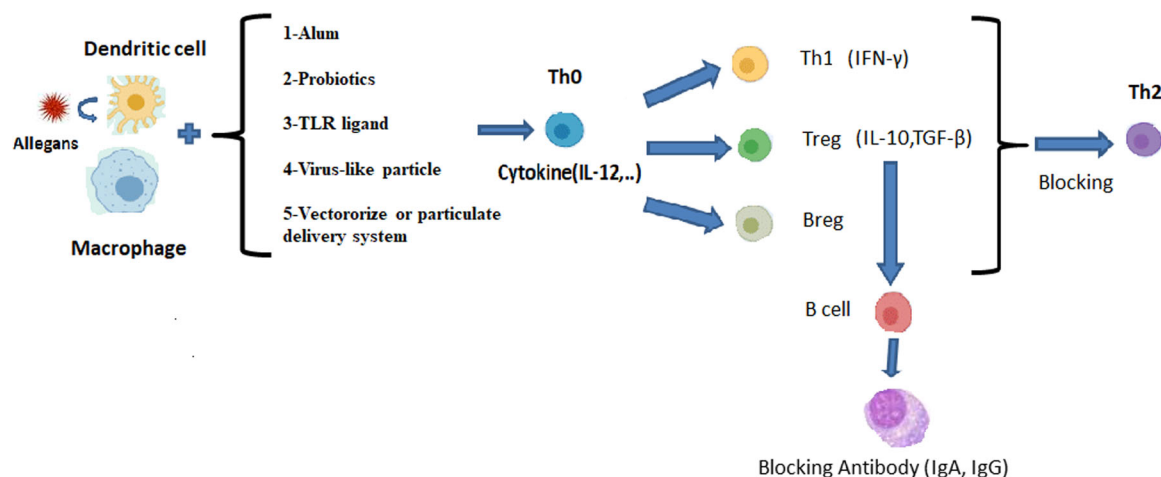


FIGURE 2 Immunologic mechanisms of allergen-specific immunotherapy and the immune potentiators or adjuvants used in clinical settings. In this immunotherapy, as shown in the figure, different adjuvants are used by main allergen stimulated Th1 and Treg and Breg cells, which cause different cytokine-blocking Th2 responses. These cells cause IgG and IgA blocking antibodies, that is, Treg (regulatory T cell) and Breg (regulatory B cell). IFN- γ , interferon- γ ; Ig, Immunoglobulin; IL, interleukin; TGF- β , transforming growth factor- β ; TLR, Toll-like receptor

Vogelbruch et al., 2000). In addition, some recently reported new drawbacks include slight initiation of cellular immunity, a tendency to provoke unwanted IgE responses, recurrent injections, and inefficiency for the stimulation of antiviral immunity (Wilcock et al., 2004).

Calcium phosphate

Calcium salts such as calcium phosphate can replace aluminum adjuvants since they have positive effects, while they are harmless and efficient (R. K. Gupta, Rost, Relyveld, & Siber, 1995). This is a natural component of the human body and is unusually endured and freely resorbed (Jiang, Premachandra, Johnston, & Hem, 2004). Calcium phosphate acts mostly by maintaining creation at the location of injection, and by directing the antigen to antigen-expressing cells as particulate antigens (R. K. Gupta et al., 1995). As calcium phosphate stimulates high levels of IgG antibodies and does not provoke IgE fabrication, it may induce less IL-4-mediated T-cells than aluminum adjuvants in humans and animals, so they are largely used for subcutaneous allergic vaccines (Moingeon, 2012; Petrovsky & Aguilar, 2004).

Emulsions component

This group includes oil-in-water or water-in-oil emulsions such as Freund's incomplete adjuvant (Byars & Allison, 1990). The mechanism of action of adjuvant emulsions involves the attainment of maintenance at the injection site, permitting the relaxed release of the antigen, and stimulating antibody-creating plasma cells (Freund, 1956). Commonly, allergens are combined in a water-phase, followed by the addition of oil and a combining agent to form an emulsion. This allergen dose forms frequently have a good immunogenic outline, with great efficacy, and prohibited treatment-induced anaphylactic side effects (Aguilar & Rodriguez, 2007). Overall, common side effects of emulsions include inflammatory responses, ulcers, and granulomas, as well as toxicity, which have restricted the utilization of emulsions in long-standing human prophylactic vaccines (Aguilar & Rodriguez, 2007; Chauhan, Tiwari, Iype, & Jain, 2017).

Liposome

Liposomes are artificial spheres in the submicron size (Allison & Gregoriadis, 1974). The bilayer phospholipids structure permits the encapsulation of hydrophilic antigens (Kersten & Crommelin, 2003). A liposome's features include nontoxicity, biodegradability, and biocompatibility, which makes them appropriate for adjuvant action (Immunopotentiators) as well as for delivery of antigens (Aguilar & Rodriguez, 2007). The better immunomodulatory action of antigens transported by liposomes may be because of their relaxed and continued release, and slower clearance of the captured protein (Childers et al., 2000). The encapsulated allergen in liposomes has been shown to increase specific immune response (Lutsiak, Sosnowski, Wishart, Kwon, & Samuel, 1998). However, some restriction of liposomes such as constancy, low stability, production, and class assurance complications seem to have been the main factors limiting the usage of these

substances as adjuvants in humans (Aguilar & Rodriguez, 2007; des Rieux, Fievez, Garinot, Schneider, & Pr  at, 2006).

Immune-stimulating complexes

Immune-stimulating complex (ISCOM), contain saponin, cholesterol, and phospholipids (des Rieux et al., 2006). The adjuvanticity and immune-modulating actions of ISCOM are due to the saponin (Kersten, Spiekstra, Beuvery, & Crommelin, 1991). ISCOMs-incorporated antigens can induce all features of immune responses (Sch  ll et al., 2005). Overall, ISCOMS have an extensive variety of immune activities, such as stimulation of APC, initiation of improved MHC II expression, construction of cytokines, mainly IL-5, IL-10, IL-2, IL-12, and IFN- γ (Sj  lander, van't Land, & Bengtsson, 1997), facilitating antibody reactions (sIgA, IgG1, IgG2a), and CD8+ and CD4+ T-cell responses (Maloy et al., 1995). Based on numerous studies, ISCOMS are strong activators of Th1 cells in murine, so they may be useful in type I allergy management (Sch  ll et al., 2005).

Virus-like particles

Virus-like particles (VLPs) are inactive, blank capsids of viruses, which contain no DNA/RNA from the virus itself (Antonis et al., 2006). These particles are able to stimulate robust B-cell responses, even in the nonexistence of adjuvants (Storni et al., 2004). VLP-based antigens are significantly taken up by DC, and prompt strong IgG responses after parenteral, mucosal, and transcutaneous immunizations (Young et al., 2006).

Toll-like receptor ligands

Some adjuvants contain "inflammatory hazard signals" or "pathogen-associated molecular patterns" recognized on the cells by pathogen-associated receptors, containing C-type lectin receptors, Nod-like receptors, and Toll-like receptors (TLRs; Oleszycka & Lavelle, 2014; O'Neill, Golenbock, & Bowie, 2013). These low-molecular-weight artificial mixtures are capable of binding to TLRs on APC and triggering nuclear factor- κ B, resulting in the appearance of numerous cytokines and costimulatory molecules (Francis & Durham, 2004). When used as adjuvants, TLR ligands contribute to reducing airway inflammation in murine models of asthma (Taher, van Esch, Hofman, Henricks, & van Oosterhout, 2008). Several of those immunopotentiators, affecting the Th1 or Treg responses, have been explored in humans in SCIT (Mothes et al., 2003).

Cytosine-phosphate-guanine oligonucleotides

Synthetic oligonucleotides, containing immunostimulatory unmethylated cytosine-phosphate-guanine motifs (CpG; immunostimulatory sequence [ISS]) can be used as an adjuvant for the division to the Th1-type immune response (Fonseca & Kline, 2009; Pulsawat et al., 2013). Allergen conjugation with ISS resulted in the improvement of its immunogenicity and furthermore decreased their allergenicity (Tulic et al., 2004). The CpGs, defined as immune modulators (adjuvants), stimulate numerous effects in the innate immune system, including stimulation of Th1- and Treg responses and the activation of DCs. These effects lead to the creation of special cytokines of Th1 and overwhelm the manipulation of allergic

responses due to Th2 (Fonseca & Kline, 2009; Kline & Krieg, 2008). Moreover, the CpGs prevent the *in vitro* unplanned IgE production by allergic people, and prompt peripheral blood mononuclear cells (PBMCs) to create IFN- γ , IL-12, and IL-18 (Bohle, Jahn-Schmid, Maurer, Kraft, & Ebner, 1999).

Monophosphoryl lipid A

MPL is a new generation of soluble adjuvants, produced from the lipopolysaccharide membrane of *Salmonella minnesota*, which is capable of stimulating a robust innate immune reaction via TLR-4 and TLR-2 (Fili, Cardilicchia, Maggi, & Parronchi, 2014). These constituents have possible benefits for use in SIT as an adjuvant because of their capability to increase the activation of DCs as well as T cells, which stimulates the creation of IL-12, TNF- α , and IL-10, prompting Th1 responses (Francis & Durham, 2004; Mothes et al., 2003). Furthermore, MPL has been revealed to increase both systemic and mucosal immunity after intranasal usage (Francis & Durham, 2004). *In vitro*, MPLA changes the allergen-irritated Th2-cell responses to "protective" Th1 in a monocyte-dependent mode (Puggioni, Durham, & Francis, 2005), while, *in vivo*, it decreases basophil stimulation and significantly amplifies IgE production, aggregating IgG4 obstructive Abs and IgG2 (Mothes et al., 2003).

Imidazoquinolines

Imidazoquinolines (IMQs) are low-molecular-weight mixtures that have powerful antitumoral and antiviral effects in animal models (Tomai et al., 1995). Therefore, a conceivable usage as adjuvants in the immunotherapy of Th2-mediated diseases was visualized (Vasilakos & Tomai, 2013). The stimulation of IFN- α from IL-12 and plasmacytoid DCs from monocytes and monocyte-derived DCs, clarify the variation of Th2 responses separately, but the benefits of these compounds for immunotherapy of allergy and asthma overcomes the simple Th1-stimulating properties (Xirakia et al., 2010). *In vitro*, as a modified Imidazoquinolines when joined with the major allergen of Der p2, it shifted allergen-specific Th2 cells toward the Th1/Th0 phenotype, downregulating Treg and IL-4 production (Fili et al., 2013).

Bacterial products

Mycobacteria are extremely immunostimulatory and can induce robust IFN- γ responses, and thus, could possibly have healing effects for allergy and asthma (Heit, Schmitz, Haas, Busch, & Wagner, 2007). Heat-killed mycobacterium vaccine has formerly been shown to effectively cure children with moderate to severe atopic dermatitis (Molavi et al., 2010). It has also been found that in a murine model of allergic asthma, the heat-killed M vaccine can stimulate a population of regulatory cells (Prasad et al., 2011).

Probiotic

World Health Organization and the Food and Agriculture Organization of the United Nations define probiotics as "live microorganisms, which, delivered in suitable quantities as a part of food, create a beneficial health influence" (Özdemir, 2010). In contrast, food

proteins have no ability to trigger the APC and are poorly immunogenic (Pan et al., 2010). It has been proposed that lactobacilli may act as adjuvants, which means that they would improve immune responses to other unrelated antigens, directed concurrently (Tripathi & Giri, 2014). Probiotics with different mechanisms help maintain hemostasis in allergic diseases, such as the balance between native microbiota, improvement of gut barrier functions, regulation of inflammatory mediators, and the development of the immune system (Hajavi, Esmaeili et al., 2019).

Amino acid-based particles

Cationic peptides, such as protamine, are arginine-rich peptides (4 kDa; Junghans, Kreuter, & Zimmer, 2001). Protamine has now been evaluated for vaccination in a BALB/c mouse model of bee venom allergy (J. M. M. Gómez et al., 2007). Poly (L-leucine-block-L-glutamate) is another amino acid-based particle with unexpected self-assembling characteristics for drug delivery (Constancis et al., 1999). Polymers of A:D-glutamic acid: D-lysine were connected to small ragweed extract and used for parenteral immunotherapy of ragweed-allergic patients (Butterfield, Gleich, Yunginger, Zimmermann, & Reed, 1981). The medical outcome strangely reduced in the groups treated with allergen integrated into particles. However, despite these positive effects, serum levels of IgE (in parallel to IgG) increased, while minor systemic hostile reactions were also observed.

Carbohydrate-based particles

Carbohydrate-based particles can bind antigens, mitigating their immunological characterization (Francis & Durham, 2004).

5 | VECTOR-BASED OR PARTICULATE DELIVERY SYSTEM

The clear need for enhanced and improved adjuvants has resulted in the development of controlled delivery systems (Gamazo et al., 2014). Numerous well-studied adjuvants can be included in the group of "particulate antigen delivery systems," such as liposomes, nanobeads, polymeric microspheres, VLPs, and ISCOMs. Vector-based adjuvants have been broadly used as transporters for DNA and protein subunit vaccines (Bramwell & Perrie, 2005).

5.1 | Polymeric NPs-based allergen-delivery systems

NPs are foreign ingredients, which can interact with the immune system, and control its actions. They could be recognized by the immune system, thereby stimulating immunosuppression or immunostimulation when used as nanomedicine. NPs that trigger the immune system might be used as vaccines, or vaccine adjuvants (Jiao, Li, Mu, & Zhang, 2014). Presently, NP-based allergen-delivery systems have gained much attention as possible adjuvants for allergen immunotherapy due to their significant role in the efficacy of allergy

vaccines (Craparo & Bondi, 2012; De Souza Rebouças et al., 2012). In recent years, numerous NP-based delivery systems have been developed, including biodegradable and nonbiodegradable polymeric carriers (Francis & Durham, 2004; Wheeler & Woroniecki, 2001).

5.2 | Biodegradable polymeric NPs

Polymeric NPs are colloidal transporters that vary in size from 10 to 1,000 nm (De Souza Rebouças et al., 2012). Among various kinds of polymers and copolymers, biodegradable polymers are the most widely used due to their excessive potential in the field of drug-delivery systems (Kalkanidis et al., 2006). These biodegradable polymers can be natural (collagen, chitosan carrageenan, gelatin alginate) or synthetic (poly(methyl meth-acrylate), poly(alkyl-cyanoacrylates), poly(lactic acids) [PLA], poly(lactide-co-glycolic acids) [PLGA], and poly(ϵ -caprolactone), [PCL]). Polymer particles used for oral immunotherapy are frequently prepared from poly lactidecoglycolide (PLGA) or poly lactide (PLA) because of their good adjuvant properties (Kanchan & Panda, 2007). Both PLA and PLGA are considered due to their great biodegradability and biocompatibility as their deprivation yields are eradicated through the Krebs cycle. This is why their use for treating human diseases has been approved by the Food and Drug Administration (FDA; Bala, Hariharan, & Kumar, 2004; Schöll, Kopp, Bohle, & Jensen-Jarolim, 2006). In addition, the nature of the polymer used to make them is an important factor in using NPs as adjuvants (Gamazo et al., 2014).

5.2.1 | Poly(D,L-Lactide)

PLAs are aliphatic polyesters, which are among the most extensively explored polymers approved by the FDA. It has been shown that the effect of size in antigen-loaded PLA particles is significant in moderating the immune response (Kanchan & Panda, 2007). Results by Akagi, Baba, and Akashi (2011) showed that vaccination with PLA NPs (200–600 nm) was associated with greater levels of IFN- γ production. In contrast, vaccination with PLA in larger sizes (microparticles [2–8 mm]) improved IL-4 release related to the T_H2 immune response (Akagi et al., 2011).

5.2.2 | Poly(D-lactic, L-lactic, and/or glycolic acids)

PLGA is one of the greatest efficiently used biodegradable polymers composed of one or more of three various hydroxyl acid monomers, that is, D-lactic, L-lactic, and/or glycolic acids (Mundargi, Babu, Rangaswamy, Patel, & Aminabhavi, 2008). PLGA is approved by the FDA and European Medicines Agency in numerous drug transporter systems in humans (Prokop & Davidson, 2008). These NPs can act as delivery systems for trapping an antigen, mixing diverse antigens, or, more significantly, mixing adjuvants and antigens in the same particle

(Hajavi, Ebrahimian, Sankian, Khakzad, & Hashemi, 2018). Furthermore, PLGA NPs, comprising very low doses of antigens and adjuvants, can stimulate robust T cell responses (Diwan, Elamanchili, Cao, & Samuel, 2004). The use of lesser doses of PLGA would be valuable for diminishing the probable side effects, often associated with the use of adjuvants, as well as from an economic point of view (Hamdy et al., 2008). In addition, because of the maintenance effects, and delayed continuous or pulsatile discharge of the captured antigen, as well as the efficient entrance into DCs, PLGA is considered to be a strong immunological adjuvant that might permit the decrease of currently essential promoter doses (Cleland, 1999). The encapsulation of allergens inside PLGA represents the most promising method to keep those allergens from degradation by normal proteases in the organism, by increasing their bioavailability delivered in vivo in a delayed-continuous or pulsatile way to control the resultant stimulation of the TH1 immune response, and reducing the potential for hostile events (Hajavi, Hashemi, & Sankian, 2019). Lastly, they deliver these allergens to the APCs (mainly DC), and simplify the suitable processing and presenting of antigens to the T cells.

5.2.3 | Poly(ϵ -caprolactone)

PCL is a semicrystalline, hydrophobic, biocompatible, and biodegradable polyester that can be used for the preparation of NPs (Irache, Esparza, Gamazo, Agüeros, & Espuelas, 2011). PCL particles do not produce an acidic setting that could destructively affect the antigenicity of the captured allergens or antigens (Jameela et al., 1996). A study used PLA as NPs for allergen immunotherapy, and it has been used as NP adjuvant system for vaccine development. For instance, PCL NPs composed of mucoadhesive polymers (chitosan or alginate) were used as a probable transporter for *Streptococcus equi* surface proteins. IgG levels of animal serum immunized with *S. equi* antigens, adsorbed or entrapped onto PCL NPs, were significantly better than those caused by free antigens or even free antigen adjuvants with the cholera toxin B subunit (Florindo et al., 2009). Therefore, the satisfactory outcomes obtained by different studies using these PCL-NPs in the field of vaccination suggest that these systems can be probable adjuvants in allergens.

5.2.4 | Poly(anhydrides) PVMA (Gantrez)

Besides polyesters, PVMA degradation of polyanhydrides results in less acidic and noncytotoxic product, which can develop the viability of the captured antigen (Mallapragada & Narasimhan, 2008). One of the main features of the Gantrez NPs is their capacity to improve robust bioadhesive contacts with constituents of the mucosal tissue in the gut (Arbos, Campanero, Arangoa, Renedo, & Irache, 2003). These NP constructions stimulate natural immunity, mediated through a TLR-4- and TLR-2-dependent route as well as the maturation of DC with an important upregulation of CD80, CD40, and CD86 and a predisposed TH1 response in animal studies

(Camacho et al., 2011). Furthermore, previous studies have described the capability of adjuvants based on poly(anhydride) (Gantrez®) NPs to prompt allergen-specific immune responses (S. Gómez et al., 2007; Salman, Gamazo, Agüeros, & Irache, 2007). Moreover, the packing of antigens into Gantrez NPs has shown to improve the immune responses in terms of a strong T_H1 adjuvant ability (Irache, Salman, Gomez, Espuelas, & Gamazo, 2010). Taken together, poly(anhydride) NPs are efficient inducers of immune responses, promising adjuvants, and allergen-delivery systems useful for immunotherapy (Rebouças et al., 2012).

5.2.5 | Poly(gamma-glutamic acid)

Poly(gamma-glutamic acid) (γ -PGA) is a polypeptide consisting of γ -linked glutamic acid components and α -carboxylate side chains produced by certain strains of *Bacillus* (Akagi, Kaneko, Kida, & Akashi, 2005). According to previous studies, these NPs can impact both natural and specific immune responses (Uto et al., 2011). In addition, *in vitro* studies with grass pollen allergen loaded γ -PGA, and DCs displayed an increased allergen-specific IL-10 production, and the spread of autologous CD4+ memory T cells. In contrast, IL-5, IL-4, IL-13, or IFN- γ cytokine production was unaffected. Results show that γ -PGA NPs are powerful adjuvants for SIT because of their robust ability to stimulate DCs and due to their capability to increase IL-10 production (Broos et al., 2010).

5.2.6 | Poly(vinylpyrrolidone) (PVP)

Poly(vinylpyrrolidone) (PVP), as NPs, provide a confident transfer system for proteins as they are biocompatible, preserve the reliability and biological activities of proteins, improve humoral responses, and offer a continued antibody level with one dose immunization. There are some studies that propose the possibility of using ultrafine monodisperse PVP for the immunization therapy of different allergens (Zolnik, Gonzalez-Fernandez, Sadrieh, & Dobrovol'skaia, 2010).

5.3 | Polysaccharides

5.3.1 | Chitosan

Poly(D-glucosamine), chitosan, is one of the most-explored polysaccharide for mucosal vaccine delivery (Qi, Xu, Jiang, Hu, & Zou, 2004). Chitosan has beneficial characteristics, such as high production biocompatibility, low prices, high biodegradability, the capability to preserve the immunogenicity of the antigens, and non-toxicity, along with its capability to improve the diffusion of macromolecules through the intestinal and nasal walls (Irache et al., 2011). Roy et al. (1999) have established the efficacy of oral vaccination by chitosan loaded DNA NPs in stimulating protective immunity against

peanut allergy in a mouse model. More precisely, chitosan-Ara h2 NPs allow a major reduction in the IgE levels of the serum, vascular leakage, plasma histamine, and the stimulation of particular mucosal IgA immunoglobulins (Zhu, Qian, Zhang, Tang, & Yin, 2007). Strangely, others have established the significance of chitosan particles as an allergen preparation method to treat HDM allergic mice via the intranasal route (Liu et al., 2009). An *in vivo* study using PBMCs from patients sensitized to HDM shows how CS-Phe-mPEG activates the immune response by measuring the IL-10 and IFN- γ secretions in PBMCs from these patients (Gaspar et al., 2015).

5.3.2 | Aquasomes

Aquasomes are ceramic/carbohydrate-based biodegradable and biocompatible NPs, which have shown promise as an adjuvant for a variety of antigens (Umashankar, Sachdeva, & Gulati, 2010). *In vivo* immune response after two intradermal doses with ovalbumin (OVA)-aquasomes results in a combined T_H1/T_H2 -type immune response. In these models, management with OVA-aquasomes provoked slight levels of serum histamine, IgE, and greater viability level in comparison with alum adsorbed OVA (Umashankar et al., 2010).

5.4 | Nondegradable polymeric nanoparticles (latex, silica, silver, polystyrene, gold)

Nondegradable NPs of numerous materials such as latex, gold, silver, silica, or polystyrene are being assessed as antigen transporters for stimulation of immunity (Combadière & Mahé, 2008; Ho et al., 2011). These polymers have numerous technological benefits. For instance, polystyrene NPs can be manufactured with numerous useful collections on their surface to accomplish effective conjugation with a variety of antigens. Also, when the antigen is covalently joined to the NP, it stimulates larger specific immune responses than in the cases where the antigen is absorbed (Fifis et al., 2004). Similarly, non-degradable NPs used for the purpose of immunization require consideration of features, such as poisonousness and particle accumulation in the tissues, which needs additional studies of *in vivo* clearance, as well as resolving possible adverse effects caused by its usage (Combadière & Mahé, 2008). Commonly, silver NPs (Ag NPs) might act as a transfer system for the cellular uptake of antigen due to the communication between the protein and the NPs (Xu et al., 2013). Taken together, the action of the adjuvant obtained from Ag NPs is mostly attributed to the employment and stimulation of local leukocytes (Barlow, Donaldson, MacCallum, Clouter, & Stone, 2005). Studies on mice subjected to intraperitoneal or sub-cutaneous vaccination (using model antigens OVA and bovine serum albumin) show that the adjuvant effect of Ag NPs is mostly attributed to the recruitment and beginning of peritoneal leukocytes, especially macrophages (Xu et al., 2013).

6 | CONCLUSIONS

Finally, protection features of new adjuvant/allergen preparations for usage in allergen immunotherapy remain a major concern in choosing appropriate preparations. Additional multicenter trials are required to assess novel planning in this context. The usage of nanotechnology stages, although increased in current years for immunization purposes, is developing in the field of allergen immunotherapy. Given the promising outcomes gained so far, polymeric NPs can be of attention to progress novel therapeutic plans able to develop both clinical safety and efficacy of allergen vaccines. In addition, our knowledge of the NPs communicating with the immune system has improved in recent years, but it remains insufficient. Therefore, additional studies on the immunomodulatory effects of polymeric NPs are crucial to increase our understanding, and therefore our ability, to plan improved specific and effective allergen vaccines.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

The manuscript was prepared and written by all authors equally.

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