

# What's New in Allergen Immunotherapy Patents? A Review

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**ABSTRACT:** In recent years, allergies are on the rise. The growth of allergies cases has changed the immune system's response to new pathogens. The therapy used to treat these diseases is based on allergen avoidance, pharmacotherapy and allergen-specific immunotherapy. The last one has received a lot of interest in the research field, due to the possibility of leading the patient to a cure. In this sense, new allergen immunotherapy need to be developed or improved to increase safety and efficiency. This review aims to evaluate patents published, from 2015 to July 2020, that have developed allergic immunotherapy treatment and administration routes, as well as new alternatives of vehicles, carriers and delivery systems in this context. The advance of new patents has been mostly seen in China and United States. The oral route is the most used in the development of new allergy treatments. However, due to the challenges that still exist in allergy therapy, association with other pathways is interesting to amplify the possibilities and alternatives of treatment. Thus, other routes of administration for allergen-specific immunotherapy such as topical, sublingual and intranasal have been explored in the research and industrial fields. Nevertheless, it has been observed that few studies are using these alternative administration routes, probably due to the higher cost and lack of investments. The delivery systems are also other tools that can be more explored in the allergen immunotherapy formulations. The effectiveness, safety and acceptance of this therapy depends on the development of new formulations and routes of administration.

**KEY WORDS:** allergen immunotherapy, allergy therapy, patents, routes of administration

## I. INTRODUCTION

The first case of “hay fever” was seen in 1819. This disease type and other forms of allergic disease were rare and remained so for 100 years. Allergic diseases still were rare in 1965, having their first case reports of anaphylaxis to foods, insects, and drugs in the 1960s. Nowadays, allergic diseases are common and their increase has already been noticed in developed countries. However, emerging economies and the developing world are also becoming a target. The increase in allergic diseases worldwide may be associated with the western lifestyle that influences the genetic predisposition through factors, such as hygiene hypothesis, vitamin D, microbiome, infant feeding practices and

exposure to pollutants.<sup>1</sup> Moreover, health conditions and few infections among young people also can induce the allergy diseases growth.<sup>2</sup>

The immunoglobulin E (IgE)-mediated allergies included atopic diseases, which are an exaggerated IgE mediated immune responses - asthma, rhinitis, conjunctivitis and dermatitis - and allergic diseases, which are immune responses to foreign allergens - anaphylaxis, urticaria, angioedema, food and drug allergies.<sup>3</sup> The IgE-mediated allergies (25%) and food allergy (10%) have a high prevalence.<sup>4</sup> There are risk factors that increase the development of this type of allergies, such as geographical distribution, environmental risks, pollution or socioeconomic status, genetic predisposition, or the "hygiene hypothesis."<sup>5,6</sup>

Asthma, allergic rhinitis, chronic rhinosinusitis, atopic dermatitis, and food allergies represent some of the most common chronic conditions worldwide<sup>7</sup> and can affect patients' physical and psychological health and influence patients' quality of life.<sup>8</sup> The prevalence of food allergy in the North American population is estimated at 3.9% to 8% in children and 6.6% to 10% in adults.<sup>9</sup> The number of adult-onset asthma was almost the same in Italy, with a prevalence of 4.6%. There may be a correlation between allergies, for example, 80% of patients with chronic sinusitis are also sensitized to food allergens.<sup>8</sup>

Therefore, allergic disease treatment is constantly pursued. The treatment of allergic diseases should be carried out with pharmacological and non-pharmacological procedures. The therapy is normally based on allergen avoidance, pharmacotherapy and allergen-specific immunotherapy (AIT).<sup>10</sup> The treatment type is essentially symptomatic and preventive, mainly using anti-inflammatory drugs that can interfere with the inflammatory cascade that occurs in the allergic reaction attempting to modify the disease evolution and decrease symptoms.<sup>11</sup>

Most allergy medication is administered one or more times a day, including the asymptomatic periods. Thus, adherence, adverse effects, costs, side-effects, and absence of active symptoms can be a problem, mainly in chronic conditions.<sup>7</sup> Adding these facts to the high prevalence of IgE-mediated allergies and food allergy,<sup>4</sup> the AIT is the only treatment that can change the course of allergic disease, preventing the development of severe symptoms, reducing the need for medication and preventing the development of new allergic conditions.<sup>12</sup>

Allergy immunotherapy is the oldest biological therapy for allergic diseases.<sup>7</sup> It was first used in 1911, by Noon and Freeman, for the pollinosis treatment.<sup>13</sup> The AIT is the unique disease-modifying approach for patients with allergic diseases, being more effective than pharmacotherapy in the symptoms decrease and safer than other therapies.<sup>14,15</sup> It occurs due to the AIT mode of action based on repeated administration of gradually increasing doses of the antigens in the hope of allowing safe exposure to the allergen.<sup>16</sup> The AIT can persist beyond the regular treatment period, unlike symptomatic treatment options.<sup>17</sup> The therapy induces several immunologic changes that contribute to the sustained immune-specific tolerance.<sup>7</sup> Consequently, the search for new goals in AIT therapies and the improvement of the old ones have increased.<sup>18</sup>

Thus, new therapies need to be developed or improved for these new approaches are necessary, such as allergen delivery systems or vaccines, which still need to be

explored.<sup>19</sup> Also, drug carrier systems can reduce toxicity and ensure higher physisorption of the drug into the targeted cells improving their effectiveness.<sup>20</sup> Therefore, the disclosure of patent content has been of great importance for the development, improvement and recognition of new treatment approaches, which can increase safety and maintain or increase clinical efficiency.<sup>21</sup>

Therefore, this review aims to evaluate patents that have developed allergic immunotherapy treatment and administration routes, as well as new alternatives of vehicles, carriers and delivery systems in this context.

## II. METHODS

In this present patent review, the research was carried out through Espacenet, from the European Patent Office (EPO) database, using the descriptors “allergic or allergenic or antiallergenic” and “sublingual or oral or nasal or parenteral.” The patent selection was based on the following inclusion criteria: recent patents published from 2015 to July 2020, in any language, and containing the keywords in the title or abstract. A total of 490 patents were identified for a preliminary assessment, of which 47 were excluded due to being duplicates. After reading the title and abstract, 355 patents were excluded that contained the terms Chinese medicine, herbal medicine, probiotics, and allopathy or pharmacotherapy, remaining 88 patents. Following a full reading of the patent, further 62 were excluded, and five patents were also excluded for being outside the scope of the review. Thus, the final section covered 21 patents. Beyond that, using the same criteria, a research was performed on the PubMed literature database, to compare the number of papers with the number of patents found in the patent databases. This research was conducted in September 2020. Figure 1 illustrates the guidelines used for the patent

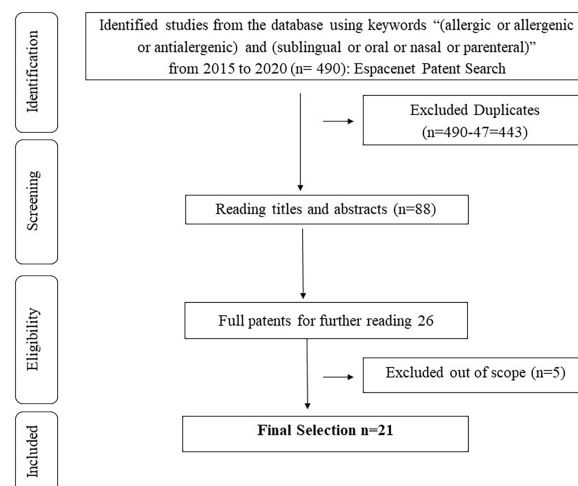


FIG. 1: Flowchart of literature search and screening

search and screening in this review, which was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In addition, the contents of the patents were classified per country and year.

### III. RESULTS AND DISCUSSION

As shown in Fig. 2, most of the patents analyzed belong to countries as the United States and China, each one with five patents. These countries culturally present more patents filed, probably, this is due to their excellent economy and investment in technology and innovation, holding intellectual property in technology researches.<sup>22</sup> In addition, five patents belong to the World Intellectual Property Organization (WIPO), which is a global forum for intellectual property (IP) services, policy, information, and cooperation, thus the patents presented in this database have a worldwide domain.

The patents publication results per year show that it has been an increase in the number of patents published since 2015, which in that same year there was only one publication that fits the selected requirements. Moreover, in 2016 and 2017, the number of publications remained the same, with two patents per year. In 2018, it had three patents, however, the peak of publication was reached in 2019 with ten patents. In addition,

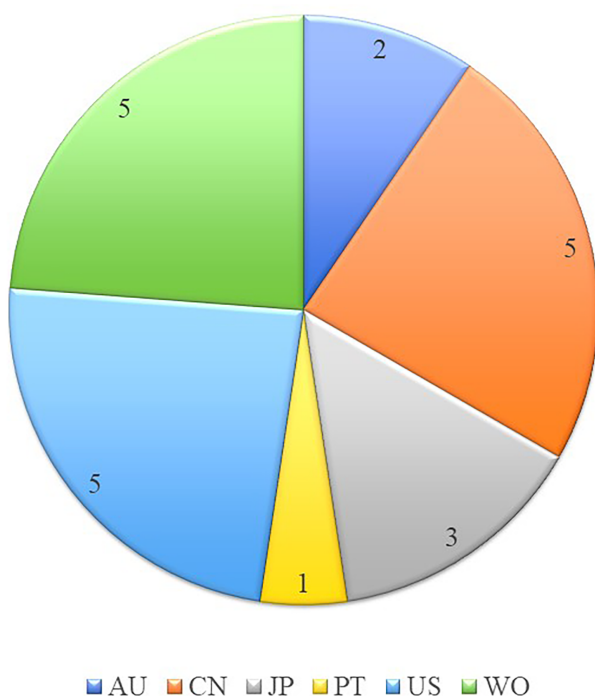


**FIG. 2:** Country of application: Australia (AU), China (CN), Japan (JP), Portugal (PT), United States (US), and World Organization (WO)

as shown in Fig. 3, in 2020, it was observed a decrease in the publications, resulting in three patents only. Probably due to the delay in the publication process and, therefore, it was not available for analysis.

The search for published scientific articles showed more results than the number of patent publications in the same period, between 2015 and July 2020. The search was made using the same combination of descriptors “allergic or allergenic or antiallergenic” and “sublingual or oral or nasal or parenteral.” The PubMed database returned 201,528 results in scientific publications. The high number of studies occurs due to the changes associated with the complexity of immunotherapy, and the precise mechanism responsible for the clinical efficacy, which has been under examination.<sup>23</sup> Also, this result can relate to other aspects such as the development of laboratory tests and biomarkers to assess the effects of the treatment, and not only related to the allergen immunotherapy.<sup>24</sup> Thus, it may explain the growth observed in the number of scientific publications to the number of patent applications. Moreover, most scientific publications are based on empirical work, while the patent information is appealing to the industrial field. However, the patent findings cover most industrial areas, including those that are not part of this work, such as traditional Chinese medicine or those outside the AIT focus.

Despite the statistics that prove the effectiveness of AIT efficiency and its progress in the last decade, this therapy still faces several problems,<sup>25</sup> such as side effects, worldwide standardization, low patient adherence. The latter probably happens due to the time of treatment throughout life and the high cost of it.<sup>15,21,25</sup> Thus, the number of allergic patients that undergo this treatment has been less than 5%,<sup>23</sup> which can be explained by the differences between regions and the socioeconomic status.<sup>18</sup>

Among the carrier systems that have been developed, it is important to mention the particles of poly(D-L-lactide-co-glycolide) acid (PLGA). It is used as a carrier system since they protect encapsulated proteins against gastrointestinal degradation, are fully biocompatible and eliminated with no polymer-specific immune response.<sup>26</sup> Another example of carrier system, the carbohydrates particles (CBPs), is used in conjunction with the allergens to prolong their exposure.

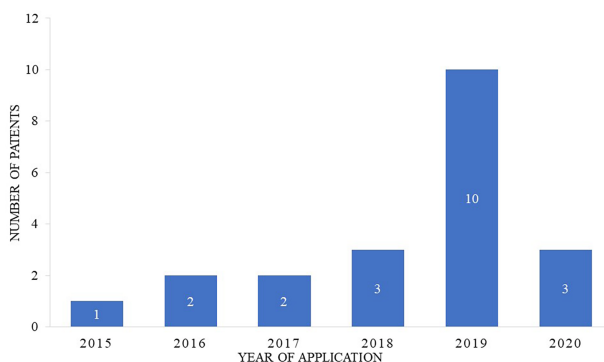


FIG. 3: Number of patents per year of application

Liposomes are also used attached to the allergens to increase their effectiveness.<sup>27</sup> Moreover, polymer nanoparticles have advantages, such as the protection of the allergen from premature degradation, co-encapsulation of immunomodulators to increase tolerogenic adaptive immune response to allergens and the facilitation of the allergen presence to the lymphoid tissue.<sup>28</sup> Despite the wide variety of technologies of this type, there is no best carrier since it is necessary to analyze the allergen, route of administration and allergic disease to choose the correct carrier.

The safety and efficacy of AIT strategies have been advanced and represent the main goals of current research efforts,<sup>25</sup> through the development of new allergen preparations, and alternative routes of administration, which will be essential for improving the implementation of AIT in the clinic.<sup>18,21,25</sup> Moreover, other approaches have been developed, such as microneedle patches,<sup>29</sup> micro-fractional lasers,<sup>30</sup> nanomedicines,<sup>31</sup> administration of probiotics.<sup>32</sup> Thus, the following section discusses the present data review according to the patent delivery systems properties, as shown in Table 1.

### A. Oral Route

Oral immunotherapy (OIT) has been used in research settings for the past years,<sup>33</sup> which has an increasing clinical and scientific interest, mainly when it refers to food allergies, through the re-establish of permanent tolerance, to desensitize or to raise the threshold level of the reaction, without being painful and invasive. Moreover, the mouth is the opening for swallowing substances that could become allergens. Also, the immune cells presenting in the oral mucosa have to develop oral immune tolerance in humans.<sup>34</sup> However, the mechanisms of this therapy have not been elucidated, although some changes presented across trials. Moreover, still have unknowledge gaps, such as optimal dose selection, and immune response changes leading to sustained unresponsiveness, as well as the possible returns of the level of reactivity.<sup>35,36</sup>

Currently, pharmaceutical and biotechnological research defines protein and peptide drug delivery systems as important therapeutic innovations. The effective and potent action of proteins/peptides makes them the drugs of choice for the treatment of numerous diseases.<sup>37</sup> Blanchard et al. published an invention based on newly identified peptides for use in the induction of oral tolerance in young mammals, in cases of cow milk allergy. The peptide identified was P-lactoglobulin, which is hypoallergenic, but retains the capability to induce tolerance to the native protein and can modulate the immune response to allergens. The invention peptides are synthetics, may be administered in their pure form or the form of a pharmaceutical composition and a composition comprising between 25 and 250 µg of peptide per gram of dry composition. The efficacy of the invention in mice sensitization was assessed by quantitative measurements of β-lactoglobulin (BLG)-specific IgE.<sup>38</sup> The absence of allergen-specific IgE provides a reliable biomarker with high specificity for the resolution of allergy. This indicator still has low sensitivity, because the clinical allergy can resolve before allergen-specific IgE becomes negative.<sup>39</sup>

TABLE 1: Allergen immunotherapy patents technical information

| Patent number                     | Country | Year | Formulation and dose                                   | Compounds                                                                       | Use indication            | Tests and methods                                                                                                                                       |
|-----------------------------------|---------|------|--------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral route                        |         |      |                                                        |                                                                                 |                           |                                                                                                                                                         |
| AU2013407963B2                    | AU      | 2019 | 25–250 µg peptide per gram of dry composition          | Synthetics peptides                                                             | Cow's milk allergy        | Mice sensitization measured by BLG-specific IgE antibodies on individual serum samples                                                                  |
| CN110419733A                      | CN      | 2019 | Neohesperidin dihydrochalcone                          | Neohesperidin dihydrochalcone                                                   | Ovalbumin (OVA) allergy   | Effectiveness in mouse model                                                                                                                            |
| US2019175724A1                    | USA     | 2019 | Hypo-allergenic proteins                               | Preparation of cross-linked caseinate                                           | Milk protein allergy      | Mouse model sensitization experiments                                                                                                                   |
| US2019060443A1                    | USA     | 2019 | Allergen                                               | Allergen                                                                        | Allergic diseases         | <i>In vivo</i> effectiveness of the treatment                                                                                                           |
| WO2019086662A2;<br>WO2019086662A3 | WIPO    | 2019 | Allergenic proteins and particularly to peanut protein | Granules comprising allergenic protein, humectant, binder, filler and lubricant | Peanut allergy and others | Process of production of the OIT; stability of dose formulations; taste masking ( <i>in vivo</i> )                                                      |
| WO2020037151A1                    | WIPO    | 2020 | Peanut protein 2043mg cumulative                       | Peanut protein                                                                  | Peanut allergy            | Up-dosing phase and a maintenance phase, administering on a non-daily basis a maintenance phase dose during at least a portion of the maintenance phase |
| US2020038466A1                    | WIPO    | 2020 | Gastrointestinal release capsules, peanut composition  | Gastrointestinal release capsules, peanut composition                           | Peanut allergy            | Process of composition and <i>in vivo</i> tests                                                                                                         |

TABLE 1: (continued)

| Patent number              | Country | Year | Formulation and dose                                                                       | Compounds                                                                                                            | Use indication                                             | Tests and methods                                                                                                                                                                |
|----------------------------|---------|------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral and other routes      |         |      |                                                                                            |                                                                                                                      |                                                            |                                                                                                                                                                                  |
| CN104491858A               | CN      | 2015 | Liquid pharmaceutical containing animal fur dander allergens.                              | Animal dander allergen protein                                                                                       | Allergy to animal hair                                     | Can f1 in dog dander, Fel dd1 in cat dander, Equc1 and Equc2 in horse dander, cow dander Bosd2 and Bosd5, Oryc1 in rabbit dander, Musm1 in mouse dander, rat Ratn1 in rat dander |
| WO2016142448A1             | WIPO    | 2016 | Two inactivated bacteria suspensions and at least two mixture of allergen-specific extract | Two inactivated bacteria suspensions and at least two mixture of allergen-specific extract                           | Combined anti-allergic treatment for respiratory allergies | Process of production of the different compositions                                                                                                                              |
| JP2017141170A              | JP      | 2017 | Soybean saponin                                                                            | Soybean saponin                                                                                                      | Allergic contact dermatitis                                | Evaluation of suppression of allergic contact dermatitis in mouse model                                                                                                          |
| WO2019070631A1             | WIPO    | 2019 | Injections                                                                                 | Cleaned pollen grains                                                                                                | Respiratory and other allergies                            | Available in animal models                                                                                                                                                       |
| Topical route: oral mucosa |         |      |                                                                                            |                                                                                                                      |                                                            |                                                                                                                                                                                  |
| PT2563316T                 | PT      | 2019 | Toothpaste                                                                                 | One or more allergen, vegetable glycerin; sorbitol; hydrated silica; purified water; xylitol; carrageenan; lauril-42 | Allergy cronic                                             | N.S                                                                                                                                                                              |

TABLE 1: (continued)

|                             |     |      |                                                                |                                                                                                                                                                                                    |                   |                                                                                                                                                                                                            |
|-----------------------------|-----|------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| US2020046828A1              | USA | 2020 | Toothpaste                                                     | Allergen extract;<br>binder comprises;<br>surface active<br>agent; abrasive<br>agent; humectant;<br>water; preservative;<br>flavoring agent;<br>opacifier; coloring<br>agent; anti-caries<br>agent | Atopic allergies  | N.S                                                                                                                                                                                                        |
| Topical route: nasal mucosa |     |      |                                                                |                                                                                                                                                                                                    |                   |                                                                                                                                                                                                            |
| US2016367604A1              | USA | 2016 | Egg yolk oil and<br>benzopyrene-<br>eliminated egg<br>yolk oil | Egg yolk oil                                                                                                                                                                                       | Allergic rhinitis | Reduction of<br>lymphocyte<br>inflammatory<br>cytokines IL-4 levels<br>in model mice                                                                                                                       |
| Intranasal route            |     |      |                                                                |                                                                                                                                                                                                    |                   |                                                                                                                                                                                                            |
| CN108066353A                | CN  | 2018 | 25 mg/mL and 50<br>mg/mL of naritirun<br>solution              | Naritirun                                                                                                                                                                                          | Allergic asthma   | Levels of IgE and<br>IgG1 immunoglobulin<br>in the serum; the<br>levels of IL-4, IL-5<br>and TNF- $\gamma$ in the<br>alveolar lavage fluid;<br>detect the lymphocyte<br>CD4 cells and CD8 in<br>mice model |

TABLE 1: (continued)

| Patent number    | Country | Year | Formulation and dose              | Compounds                                                                                                                             | Use indication                                                         | Tests and methods                                                                                                                                                                         |
|------------------|---------|------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sublingual route |         |      |                                   |                                                                                                                                       |                                                                        |                                                                                                                                                                                           |
| CN108607096A     | CN      | 2018 | Dust mite allergen and pigments   | Dust mite allergen pigments, <i>Dermatophagoides pteronyssinus</i> , <i>Dermatophagoides farinae</i> allergen or a mixture of the two | Dust mites allergy                                                     | Compounds and methods for preparation                                                                                                                                                     |
| WO2019189676A1   | WIPO    | 2019 | Hyaluronic acid and mite allergen | Hyaluronic acid and mite allergen                                                                                                     | Asthma                                                                 | Mite allergen-induced chronic asthma model mouse, and an inhibitory effect on eosinophilic airway inflammation; suppression of IL-5 and IL-13 production locally in the respiratory tract |
| JP2019196379A    | JP      | 2019 | Sublingual tablet                 | <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i> allergen extracts                                           | House dust mite allergy and allergic asthma caused by house dust mites | The amount of IgE produced in response to the allergens and their content in natural extracts                                                                                             |

OIT, oral immunotherapy; WIPO, World Intellectual Property Organization. AU, Australia; CN, China; JP, Japan; PT, Portugal; USA, United States of America.

Moreover, Gors-Van et al. developed hypo-allergenic cross-linked proteins used to prevent an allergy against milk proteins, inducing oral tolerance for casein or caseinate. Cross-linked caseinate or cross-linked casein and combinations, carbohydrates, fat, and oligosaccharides compounded the invention. Therefore, the mouse model sensitization experiments resulted in a reduction of mouse mast cell protease (MCP-1) concentration, as well as a decrease in specific serum IgE, indicating the lack in the induction of intestinal mast cell degranulation.<sup>40</sup>

Adelman disclosed an invention to treat peanut allergy using oral immunotherapy with an up-dosing phase and a maintenance phase, which may be longer than 24 weeks. Peanut protein is used as therapy, with the maintenance dose between 200 mg and 1000 mg, presenting a dose of 2043 cumulative peanut protein. The dose administered during the up-dosing phase comprises between 0.5 mg and 5.000 mg.<sup>41</sup> Beyond that, the invention can include non-daily administrations of the maintenance phase. Furthermore, Frodsham et al. also reported a patent based on allergies to food, mainly to peanut protein formulations. Granule comprising allergenic protein, a humectant, a binder, a filler, and a lubricant composed this invention. Moreover, this formulation can be filled into a sachet or drinking straw, capsule, or tablet, used as drug carrier systems for improving the efficiency of the invention, through the reaching of the target region.<sup>42</sup> The clinical trial proposed by Nadeau and collaborators is based on the same approach and presented promising results.<sup>43</sup>

Most of the OIT formulations are based on taking a daily dose of allergen, starting with a low one. Several increasing doses are administered on the first day, followed by a build-up phase during the last tolerated dose on the first phase, continuing daily with dose increases performed every one to two weeks until the maintenance dose is achieved. Consequently, daily dosing is continued in the maintenance phase.<sup>44</sup> This therapy is a temporary phase of protection, which is only maintained as long as the regular OIT dosage is continued and the protection is lost on discontinuation of regular allergen exposure.<sup>45</sup>

Evrard et al. also published an invention to treat peanut allergy. The formulation relates to a gastrointestinal release capsule compounded by a core, a shell, and a peanut composition, causing the desensitization and inducing tolerance to peanuts in the peanut-allergic subject. Due to the importance of the contact between the peanut substance and the immune cells of the stomach and small intestine, the capsules are used as a drug carrier system to maintain the integrity of the substance before reaching the target. The capsule comprises 10 mg to 1000 mg, and the desensitizing phase consists of a daily administration of 10 mg to 2 g for 28 weeks. Then, the maintenance phase consisted of a daily dose of peanut between 2 g and 5 g, which were established through tests. Thus, the invention resulted in desensitization, due to the measure and decrease of the antibodies IgE and specific immunoglobulin G4 (IgG4),<sup>46</sup> which is associated with basophil activation and is predictive of sustained outcomes.<sup>39</sup> An approach like that is also seen in the clinical trial developed by Aimmune Therapeutics Inc, presenting good results.<sup>47</sup>

Due to the fact that the majority of children with egg allergy are expected to outgrow their allergy in about 20% and it will persist into adulthood,<sup>48</sup> Niu et al. proposed an

invention based on neohesperidin dihydrochalcone and its promotion and maintenance of oral tolerance. The neohesperidin dihydrochalcone has the advantage of alleviating the symptoms of weight loss and hypothermia caused by ovalbumin (OVA) allergy. The invention determined the presence of IgE, immunoglobulin G1 (IgG1), and MCP-1 in the serum on different doses, resulting in the decrease of these indicators, certifying the effectiveness of the neohesperidin dihydrochalcone, and the successful stabilization of the oral immune tolerance in the mouse model.<sup>49</sup>

## B. Oral and Other Routes

OIT can successfully desensitize many food allergies, however, clinical tolerance diminishes overtime on discontinuation or low-dose maintenance of the food.<sup>50</sup> The tolerance is established by the expression of allergens as possible means of antigen delivery immunotherapy of allergic diseases that could address issues of convenience and compliance.<sup>51</sup> To guarantee more effectiveness, safer, and convenient immunotherapy for allergic diseases, other routes can be associated with oral immunotherapy.

Then, Garcia-Ibanez related composition and methods for the treatment of allergic diseases. An allergen composes the invention and is delivered in two phases, buildup and maintenance. The first embodiment includes a sublingual administration, followed by a dose on the oral vestibular space. The allergen dosage could be increased over time, which permits a gradual rise in the patient's tolerance to the allergen. The first administration treatment phase is over a while, then the second dosage of the allergen remains constant over time during twelve weeks. Moreover, another embodiment provides a serum, which includes at least one allergen. The serum is self-administered by the patient following the same method as the first embodiment.<sup>52</sup>

The invention induces a decrease in eosinophilic infiltrates and allergen-specific lymphocyte type 2 helper (Th2) responses, in parallel with induction of systemic type 1 helper (Th1) and regulatory T cells (Treg) responses. Also, it decreases a specific IgE in serum and mucosa and induction of allergen-specific immunoglobulin A (IgA) and immunoglobulin G2 (IgG2). Besides that, the circadian rhythmicity affects the function of the immune system varying immunocompetent cells and cytokines, which assures a well-timed anticipatory organization of biological process, that plays a critical role in the preservation of body homeostasis and defense.<sup>52</sup>

Gill and Shakya proposed an invention to reduce or prevent food and respiratory allergies, based on a novel pollen composition. Pollen cleaned, demonstrating naturally-occurring allergic plant protein, and a therapeutically effective amount of allergen loaded into the cleaned pollen compose the formulation. The device also is adapted for prophylactic use as a preventive vaccine.<sup>53</sup> The use of systemically via injections therapy is based on the multiple injections of increasing doses of a specific allergen until a therapeutic level is achieved. Besides that, preventive vaccination can begin in healthy individuals to block allergy development.<sup>54,55</sup> According to Li, bee pollen can work to improve human health due to its nutritional components, which can increase the immune response.<sup>56</sup>

Quin provided a liquid pharmaceutical composition containing an animal fur chip allergen for stabilizing hair animal allergy, which can be used as a treatment or diagnostic. The allergens are derived from cats (Fel d1), dogs (Can f1), horses (Equc1 and Equc2), bovine (Bosd2 and Bosd5), rabbit (Musm1), rat (Ratn1), and laboratory animals (Oryc1), as well as the single- component animal dander allergen protein. The groups that received the preparation had a decrease of 40.7% in the total protein concentration, and a reduction of 53.2% in the main allergen protein concentration.<sup>57</sup> Moreover, the formulation can be administered through other routes beyond the oral, such as sublingual, which has long-term effects, and provides a regular self-administration;<sup>23</sup> subcutaneous injections, being the most commonly used; skin pricking agents, that guarantees a safely self-administration without pain;<sup>29</sup> and aerosols and nasal preparations, providing dose reliability, emitting an accurate and consistent dose.<sup>58</sup>

Katase et al. reported on an allergic contact dermatitis inhibitor, composed of soybean saponin. The active principle of the formulation has an excellent allergic suppressing effect, providing a preparation to act against dermatitis that can be administered through oral or external application in the skin.<sup>59</sup> The transdermal route provides drug carrier systems, such as gel and cream, which adhere to the skin and sustained drug release without passing through the first-pass metabolism.<sup>60</sup> The chosen routes are painless and guarantee the user's self-administration. Transdermal delivery is an excellent choice because the skin is an important proinflammatory organ that has essential immunological functions.<sup>61</sup> Moreover, Lorz et al. also proposed to treat dermatitis with saponin derived from a potential medicinal plant, resulting in the effective treatment of many skin diseases, also proving to be nontoxic, less expensive, and natural therapy.<sup>62</sup>

The percentage of respiratory allergies that affect the population is large. Allergic asthma affects 18.7 million American adults and 6.8 million children, and 20% of the European population.<sup>63</sup> New technologies must develop to increase the population's quality of life suffering from this disease. Ballini and Silvi invented a kit of compositions and a combined anti-allergic therapy for the treatment of respiratory allergies, such as allergic asthma and rhinoconjunctivitis. A two to 40 weeks' inductive phase based on the administration of at least two inactivated bacteria suspensions and a specific phase of at least three weeks, comprising the administration of at least two mixtures of an allergen-specific extract and an inactivated bacteria suspension. Both of the phases can be administered through the oral, nasal, or oral mucosa.<sup>64</sup> Moreover, the invention has structured the modulation of the innate immune system proportionate by the bacteria products.<sup>65</sup>

### **C. Topical Route: Oral Mucosa**

The exposition of the oral mucosa to foreign agents occurs constantly. The allergens can generate cells of the innate arm of the immune system. Its epithelium provides the outermost barrier, protecting deeper tissues from physical damage, invasion by microorganisms with their associated antigens and toxins, penetration of water, and water-soluble molecules, including habit-related agents. The oral mucosa immunity dysregulation

develops oral immunopathogenic reactions or infections. New approaches have been developed to avoid the hypersensitivity immune responses activation to allergies.<sup>66,67</sup>

Cedric developed immunotherapy for the oral mucosal area allergy targeted, mainly to the area where the ratio of dendritic cells to mast cells is high. Toothpaste, a mouthwash, a mouth spray, or a flexible bag and at least one allergen provided as natural or allergen extract composed the formulation.<sup>68</sup> These drug carrier systems are mostly used because they are painless and for having direct contact with oral mucosa.<sup>69</sup> One or more allergens, vegetable glycerin, sorbitol, hydrated silica, purified water, xylitol, carrageenan, and lauryl-42 comprises the invention. Also, it provides a soft pouch inserted into the oral cavity in the vestibular mucosa, which causes allergic desensitization. Thus, the composition has a prolonged-release action, avoiding continuous contact with the oral mucosa area close to high concentrations of mast cells associated with lymph nodes.<sup>68</sup>

Berglund and Nelson also described a toothpaste to treat and inhibit topical allergies. The formulation comprises allergens or allergic extracts suspended in a solution compounded by sugar alcohol and a viscosity modifier. The combined allergens for the same purpose in formulations that use oral products as a drug carrier may provide higher sustained contact of the active principle and the target tissue. The invention tests are based on the dust mite allergen extract and extract in glycerol suspension for 180 days. Thus, toothpaste formulations present physical stability and do not exhibit phase separation resulting in water or flavor separation.<sup>70</sup>

#### **D. Topical Route: Nasal Mucosa**

Local nasal immunotherapy (LNIT) has been investigated since 1970, first in the United States and afterward in Italy. LNIT administration is based on gradually increasing amounts of the allergen into the nasal cavity until a maintenance dose is reached to achieve a hypersensitization and reduce symptoms due to natural exposure to the allergen.<sup>71</sup> This route has been chosen due to the mucosal tissue sustenance of the microbiota balance and the facilitation of inducing tolerance against environmental and dietary antigens meanwhile mediating effector responses against pathogens.<sup>72</sup> However, LNIT has shown effectiveness only in patients with rhinitis symptoms and rhinosinusitis, whose treatment is in conjunction with other modalities.<sup>73,74</sup> Moreover, this therapy also requires a particular technique of administration. Consequently, the LNIT has been progressively decreasing.<sup>24</sup>

Dong proposed medication and a method for allergic rhinitis treatment, using egg yolk oil and benzopyrene-eliminated, topically smearing in the nasal cavity. The effect of egg yolk oil on allergic rhinitis resulted in the improvement of the symptoms as well as the reduction of the levels of interleukin 4 (IL-4) and IgE antibody in model mice tests.<sup>75</sup> According to the literature, egg-derived lipids and their metabolites can affect the immune status of the body due to their large biological activities, such as antioxidant, memory improvement, and immune regulation, which are associated with the structure of the phospholipids.<sup>76</sup>

## E. Intranasal Route

The first line defensive organ is the respiratory epithelium, which can resist the invasion of various respiratory pathogens, activating the innate immune system as a defense mechanism, preventing infection.<sup>75</sup> Therefore, intranasal therapies are first-line treatments for moderate to severe respiratory allergies, such as intranasal corticosteroids and antihistamines.<sup>77,78</sup> The nasal mucosa presents a large number of immune cells and a higher capacity to develop an immune response, being an essential target to new technologies in the allergies treatment.<sup>72</sup>

Thus, Liu et al. provided a mechanism for the use of naringin. This substance inhibits allergic asthma induced by OVA, through the differentiation of T cells. The formulation has a concentration of 25 mg/mL and 50 mg/mL of naritirun solution, and the administration is through the intranasal route. The invention detected the levels of antigen-specific antibodies IgE and IgG1 in the serum as well as the levels of IL-4, interleukin 5 (IL-5), and gamma interferon (TNF- $\gamma$ ) in the alveolar lavage fluid. Also, it detected the lymphocyte CD4 and CD8 cells. Thus, the results guarantee a decrease in these indicators, proving the effectiveness of this product.<sup>79</sup>

## F. Sublingual Route

Although this therapy has been used around the world for over a century, only in 2014 the US Food and Drug Administration approved three sublingual immunotherapy (SLIT) tablets for the treatment of allergic rhinitis, with or without allergic conjunctivitis. SLIT is a safe and effective therapeutic modality for allergic diseases, based on the disease properties modification having the potential to cure allergies. Despite this, it does not have systemic complication profile,<sup>80</sup> invasiveness of subcutaneous immunotherapy and frequent visits.<sup>81,82</sup> The SLIT administration should achieve an immediate systemic absorption of the allergen through sublingual mucosa. However, this absorption can be absent or negligible.<sup>83</sup>

Katoh described a mouse model of SLIT using hyaluronic acid (HA) for asthmatic patients. The device is a ligand for CD44 that can suppress the IL-5 and interleukin 3 (IL-3) production locally in the respiratory tract. This invention used a mite allergen-induced chronic asthma administered in combination with an allergen composed by HA as an active ingredient, as a tablet preparation.<sup>84</sup> OIT and SLIT formulations used this drug carrier system because of their polymer types that can increase contact with the mucosa.<sup>85</sup> The period of administration is an appropriate set conforming to the therapeutic effect. However, it recommended a long-term administration of two years or longer. The formulation resulted in an inhibitory effect on blood mite-specific IgE antibodies and the suppression of airway hypersensitivity. Alternatively, the invention can promote the transforming growth factor beta (TGF- $\beta$ )-positive regulatory T cells induction. Therefore, the use of HA brings beneficial effects in lung inflammation and airway diseases, that could be a matrix modulator, due to its products of degradation, which participates in biological processes, such as

cell-matrix signaling, tissue healing, inflammation, angiogenesis, cell proliferation, and migration.<sup>86</sup>

The patent developed by Bai et al. described the compounds and methods for the preparation of a fast disintegrating sublingual tablet vaccine, used as a drug carrier system, against dust mites' allergy. Mannitol, aspartame, pigment, and phosphate buffer component compounded the formulation provided. Thus, the resulting formulation has advantages, such as good shelling, complete sheet shape, moderate hardness, and rapid disintegration within two seconds.<sup>87</sup> Furthermore, Vazquez et al. also proposed a sublingual tablet, which can have a faster effect to treat or prevent house dust allergy and allergic asthma caused by house dust mites. The formulation comprises *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* allergen extracts to sensitize the patients with two major dust mite allergens. However, dust mites contain more than 20 different allergens, and the choice of the allergens is based on the frequency of patients sensitized to these. The production of the IgE is the immunological response of the natural extracts, which is the most essential allergen.<sup>88</sup>

SLIT is considered the cheaper, simpler, and safer treatment due to the fewer opportunities to involve systemic reactions. Because of these factors, the SLIT is commonly used in five to 65 years old patients.<sup>23,76</sup> A mechanism of SLIT is based in the oromucosal contact with allergen through the interaction of dendritic cells, Langerhans cells, and T-cells within the mucosa or in the regional lymph nodes.<sup>89</sup> Moreover, the development goals for SLIT can include the prevention of allergic symptoms, sustained clinical effect, and disease-modifying effect.<sup>83</sup>

#### IV. CONCLUSION

Several types of therapies have been developed to treat allergic diseases, such as medicines. However, the AIT remains the only curative treatment for these diseases based on the activation of the immune system. Despite this, a long period of treatment and the risk of anaphylactic shock depend on some precautions in this therapy. An alternative are the drug carrier systems that can reduce toxicity and ensure higher physisorption of the drug into the target cells improving their effectiveness.

Among the delivery systems used in the patents discussed on this review, the most used were the oral delivery systems and their combinations. However, some limitations of this route are the low adherence and possible side effects, it can decrease the treatment effectiveness and disease control. Other systems have been used to circumvent these limitations, such as topical, intranasal and sublingual routes. Moreover, there are still some allergens that do not have a good clinical response in AIT and, therefore, there is still much to be develop for the proper formulation for some antigens.

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