REVIEW

Pediatrics Sciences Journal (*PedScij*) 2025, Volume 6, Number 1: 6-12
P-ISSN: 2722-0427, E-ISSN: 2722-1474

Pediatric Sciences Journal

Published by
Pediatrics Sciences Journal

Epicutaneous immunotherapy for peanut allergy treatment in pediatrics: A literature review

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Received: 2025-01-02
Accepted: 2025-02-11
Published: 2025-03-12

ABSTRACT

Peanut allergy in children is a growing public health concern that significantly affects patients' quality of life. Although oral immunotherapy (OIT) has shown effectiveness in desensitizing allergic reactions, it is associated with a threefold increased risk of anaphylaxis compared to strict avoidance. As an alternative, epicutaneous immunotherapy (EPIT) has emerged as a promising therapy due to its favorable safety profile, ease of administration, and non-invasive nature. However, despite increasing interest in EPIT, there is still limited evidence assessing its efficacy and safety in pediatric populations. This literature review aims to summarize current findings on the mechanism of desensitization, clinical efficacy, safety, and impact on quality of life associated with EPIT in managing peanut allergy in children. Relevant articles were identified through database searches in PubMed, Cochrane, Science Direct, Scopus, and Google Scholar using Medical Subject Headings (MeSH) and keyword combinations such as "Epicutaneous Immunotherapy", "Peanut Allergy", and "Pediatric Allergy". EPIT works by delivering peanut allergens through a patch applied to intact skin. The allergen is taken up by Langerhans cells and presented to the immune system, triggering regulatory T-cell (Treg) responses that reduce allergic sensitivity. Viaskin© is the most clinically advanced EPIT delivery system currently available. Findings from clinical studies indicate that EPIT is effective in inducing desensitization, with a lower risk of systemic reactions compared to OIT. Furthermore, EPIT contributes to improved quality of life in children with peanut allergy. These results support EPIT as a promising therapeutic option for pediatric peanut allergy management.

Keywords: *Peanut Allergy, Pediatric Allergy, Epicutaneous Immunotherapy*.
Cite This Article: Fadya, V., Safira, S.S., Nabila, A.Q., Yufika, A. 2025. Epicutaneous immunotherapy for peanut allergy treatment in pediatrics: A literature review. *Pediatrics Sciences Journal* 6(1): 6-12. DOI: 10.51559/pedscij.v6i1.109

INTRODUCTION

Globally, the high incidence of peanut allergy in children remains a significant challenge. Epidemiological studies reveal that peanut allergy occurs in 1-3% of children in the world.[1] Peanut allergic reactions usually begin to manifest at the age of 4 months to 2 years and are more likely to cause severe reactions than other food allergies. Food allergies, such as those to milk, egg, wheat, and soy, usually resolve in childhood or adolescence in half of the cases.[2] Only around 20% of sufferers can naturally overcome and tolerate peanut allergy so that they do not have symptoms when they reach adulthood.[3] Genetic and environmental factors have a big influence on the emergence of peanut allergy. Genetics is estimated to be a causal factor in 81.6% of sufferers.[4]

Allergy to peanuts often occurs because they contain low-molecular-weight proteins and are resistant to heat, proteases, and denaturants. Early exposure to peanuts in children will stimulate the production of immunoglobulin E (IgE) antibodies. In sensitized individuals, IgE antibodies bind to IgE receptors on cells such as basophils and mast cells, which then triggers an allergic response.[5] Current peanut allergy treatment is to avoid eating peanuts. However, the possibility of negligence is very likely to occur, especially in children who are still unable to understand or receive information well. The worst reaction that can occur is an anaphylactic reaction.[6]

Although studies on peanut allergy therapy continue to be developed, there is still no therapy that has been proven effective for children under 4 years old.[7] In January 2020, the first oral immunotherapy (OIT) product for peanut allergy was approved by the US Food and Drug Administration (FDA).[8] Oral immunotherapy has been proven to induce desensitization[9], namely an increase in the threshold of an allergen that can cause an allergic reaction or the most significant dose that can be tolerated.[10] However, it has been shown to have a low safety level. Studies state that oral immunotherapy has a 3 times greater risk of anaphylaxis compared to conventional therapy of avoiding peanuts.[11]

Safety concerns with OIT have prompted an urgency to create alternative delivery routes. Alternative therapies being developed include sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT). SLIT is a therapeutic method that has been widely developed for allergic rhinitis, but there is very little research on its application for peanut allergy.[12] Research using SLIT administration for peanut allergy has been carried out with good efficacy and safety results, but the research is still

Table 1. Comparison of immunotherapy for allergic patients[21]

	Epicutaneous immunotherapy	Sublingual immunotherapy	Oral immunotherapy
Allergen dosage	+	++	+++
Effectivity	+ +	++	+++
Side effects	+	++	+++

limited and only carried out on small samples, so further research is needed.[13] Meanwhile, EPIT has been widely tested and developed for peanut allergy because of its better safety than OIT. Application of EPIT is done by using a patch containing the peanut allergen protein and then attaching it to the patient's skin.[14]

To date, there have been many reviews discussing the effectiveness of OIT against food allergies, especially peanuts.[15–19] However, there are still very few studies discussing EPIT specifically for peanut allergy. Therefore, this study intends to summarize the existing knowledge about the mechanisms of desensitization, efficacy, safety, and quality of life of patients after EPIT therapy. We hope that this literature review can provide new opportunities for pediatric allergy and immunology science in developing new treatments for peanut allergy in children.

METHODS

This study is a literature review that is carried out by identifying, evaluating, and interpreting research results adapted to the topic raised. The literature search process was carried out on several databases, namely PubMed, Cochrane, Science Direct, Scopus, and Google Scholar. In conducting a literature search, we used several keywords, namely "Epicutaneous Immunotherapy", "Allergen Immunotherapy", "Pediatric Allergy", and "Peanut Allergy," and synonyms using Medical Subject Headings (MeSH) and title/abstract combined with the Boolean operator ("AND" and/or "OR"). A literature search from electronic databases yielded 7781 studies. This study contains articles, scientific reports, and studies (i.e., cohort, qualitative studies, open-label, randomized controlled trials, cross-sectional), which are then assessed for relevance and reviewed for eligibility. After screening the complete text, 25 were included in the studies.

DISCUSSION

Peanut Allergy in Children

Peanut allergy is one of the most common food allergies in children and has continued to experience a significant increase in the last few decades. Currently, around 1-3% of children in the world have an allergy to peanuts. A hypothesis regarding the mechanism of peanut allergy explains that allergic sensitization to peanuts occurs through the skin, especially in children with allergic skin disorders such as atopic dermatitis. Peanut allergy often occurs throughout life, and this affects a person's quality of life.[4]

Until now, there is no standard therapy to treat food allergies except attempts to avoid foods that cause the allergy. Even though we try to prevent it, accidental consumption of food allergens often occurs and often causes severe and potentially life-threatening allergic reactions. Therefore, prevention, diagnosis, and appropriate management of patients with peanut allergy are important.[13]

Management of peanut allergy continues to be developed. In recent years, a new treatment has begun to emerge called immunotherapy. Immunotherapy is an interesting treatment for allergy patients by giving them the substance in high doses. The aim is to increase the patient's desensitization to its substance.[4]

Immunotherapy of Peanut Allergy in Children

Food allergen immunotherapy (FA-AIT) is an immunomodulatory intervention for IgE-mediated food allergy that works by repeated exposure to periodically increasing doses of allergen. There are several ways of administering food allergens, including orally, sublingually, epicutaneously, and subcutaneously.[20]

Different routes of allergen administration certainly related to the amounts of allergen given and closely affected the effectiveness and its side effects. This can be seen in Table 1. There are several differences in the characteristics of each type of allergy immunotherapy. These data are obtained from clinical trials and are based on oral immunotherapy for peanut allergy.[21]

Based on the table above, it is necessary to assess the use of immunotherapy based on three important aspects, namely allergen dosage, effectiveness, and side effects. When administering EPIT, the dose given is smaller than other immunotherapy, but the effectiveness is commensurate with sublingual administration. EPIT has fewer side effects than other immunotherapy. This proves that EPIT provides greater effectiveness than the side effects it causes. Meanwhile, oral administration with larger doses certainly provides greater effectiveness, but the side effects are also greater.[21]

Oral Immunotherapy (OIT)

The use of OIT for existing peanut allergy is in the form of defatted peanut powder. This drug is consumed in the form of capsules or sachets, which are sprinkled in food. Peanut allergy medication licensed and approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) is only a medication for children aged 4 to 17 years. Meanwhile, for ages 0 to 3 years, there is no recommended oral immunotherapy treatment.[9]

OIT involves the administration of small, gradually increasing doses of peanuts with the aim of enabling patients to eat varying amounts without reactions. Most research studies include an initial up-dosing phase (with or without a "rush" escalation), which usually lasts a few weeks or months, and a long-term maintenance phase once the desired maintenance dose is reached. OIT contraindications include uncontrolled or severe asthma, active eosinophilic esophagitis, severe gastroesophageal reflux, dysphagia or any chronic undiagnosed GI condition, inability to follow protocols or non-compliance with regular dosing, pregnancy

or breastfeeding.[22]

A study was conducted at 5 academic medical centers in the United States with participants of children aged 12 to <48 months. The study was done by administering ~500 mg of peanut protein at the start of a double-blind, placebo-controlled food challenge (DBPCFC) for 134 weeks to a maximum dose of 5000 mg at the end of the week. The study showed that 71% of participants given OIT and 2% placebo achieved desensitization at week 134. The study continued by stopping OIT administration until week 160. Only 21% of participants with OIT and 2% placebo achieved remission criteria (able to reach a maximum dose of 5000 mg at 26 weeks after discontinuation of OIT).

These results indicate that a significant number of participants with OIT who were able to achieve desensitization at week 134 were unable to tolerate the 5000mg dose at week 160 ($p<0.001$) compared to placebo participants desensitized at week 134 who all achieved remission at week 160. This study shows that giving EPIT to children before the age of 4 years has the opportunity to induce desensitization and remission of peanut allergy.[9]

Sublingual Immunotherapy (SLIT)

SLIT is indicated for individuals with a confirmed diagnosis of peanut allergy, demonstrated through clinical history and positive oral food challenges. Studies have evaluated SLIT in children aged 1 to 11 years, with some evidence supporting its use in older children and adults. SLIT may be considered for patients at risk of severe allergic reactions, aiming to reduce the severity of future exposures. SLIT is contraindicated in children with uncontrolled asthma, significant cardiovascular or respiratory conditions, and unable to commit to the regimen.[23]

A daily dose of approximately 2 mg of peanut protein is commonly used in pediatric studies. Treatment duration varies, with studies ranging from 12 months to 5 years, depending on patient response and tolerability. SLIT has been shown to induce desensitization, allowing patients to tolerate higher amounts of peanut protein without adverse reactions. The treatment is generally well-tolerated, with most adverse reactions being mild and localized. Mild symptoms include oropharyngeal itching, lip swelling, and gastrointestinal discomfort. Anaphylaxis is rare but has been reported, emphasizing the need for monitoring during treatment. SLIT is non-invasive and can be administered at home, improving patient compliance compared to other forms of immunotherapy.[23]

Peanut allergy treatment carried out in a study conducted on children aged 1 to 11 years who were given 4 mg SLIT therapy for 48 months showed that the average dose successfully consumed increased from 48 mg to 2723 mg peanut protein ($P<0.00010$) with 70% achieving clinically significant desensitization (maximum dose that can be consumed >800 mg) and 36% complete desensitization (maximum dose that can be consumed 5000 mg). Meanwhile, the average reaction per dose is 0.5%, experiencing itching in the oropharynx. There were no symptoms requiring administration of epinephrine. This study showed that SLIT provided clinically significant desensitization that persisted 17 weeks after discontinuation of therapy.[24]

In another study conducted on peanut-allergic children aged 1-11 years, extended administration of SLIT with peanut protein 2 mg/day for up to 5 years showed that 37 of 48 subjects completed SLIT for 3 to 5 years, of which 25% of subjects were successful. Following DBPCFC 5000 mg without clinical symptoms, 10 of 12 patients showed no sustained response over 2 to 4 weeks. Side effects caused by 4.8% of the dose, with temporary itching in the oropharynx. Meanwhile, side effects requiring antihistamine treatment were rare (0.21%), and no epinephrine was administered. In addition, the appearance of spots after the peanut skin test, peanut-specific IgE levels, and basophil activation decreased significantly, while peanut-specific IgG4 levels increased significantly. This shows that long-term SLIT therapy provides clinically significant desensitization.[24] Based on these two studies, it can be concluded that SLIT administration provides good desensitization results with minimal side effects.

Epicutaneous Immunotherapy (EPIT)

EPIT is administered by applying the allergen to the scarified skin in the non-vascularized epidermis layer.[25] When used, allergic side effects rarely occur when the allergen is applied through the skin, and if they do occur, the reactions are usually always mild compared to conventional SCIT.[26,27]

Epicutaneous immunotherapy is growing rapidly in use because the side effects are not as severe as OIT or SLIT. Another advantage is that in the EPIT route, keratinocytes can also be activated through physical irritation, for example, abrasion and removal of adhesive tape. Epithelial damage increases keratinocyte expression of additional molecules such as IL-1α, IL-6, and TNF-α, thereby causing the immune response to become a Th1-type response. Activation of keratinocytes is essential for creating a pro-inflammatory environment with increased Langerhans cell activation, so this makes EPIT superior to SLIT, even though both are very safe in terms of systemic side effects.[25,26] Usually, EPIT is given with a patch containing allergens with doses that will be adjusted to the patient's needs. In its development, trials, and technology development are needed to see its safety and effectiveness.[26]

Development of EPIT Technology in Peanut Allergy

Epicutaneous immunotherapy aims to induce desensitization through immune cells in the skin.[28] The most clinically advanced EPIT technology development to date comes from the Viaskin© technology platform. Viaskin© uses a patch-shaped system and contains dried original allergen extract, without additional ingredients, which is then attached to intact skin. In this technology, allergen bioavailability is facilitated by a unique system design. The allergen extract is sprayed with electrotechnology onto a film disc that is held in place by a foam ring underneath. Together, the foam ring and film disc containing the allergen form a condensation chamber. This space becomes a place for water to evaporate from the skin so that it can dissolve and release allergenic proteins from the film disc to enter the skin and facilitate

absorption into the superficial layers of the epidermis.[27]

Apart from Viaskin©, there are several other less frequently used methods for administering EPIT, such as ablative fractional laser, microneedles, and nano-assisted. Ablative fractional laser (AFL) is a method of creating microchannels in the epidermis or dermal layer to increase the transcutaneous entry of allergen solutions or powders through the formed micropores, especially for biomacromolecules. Microneedles have emerged as an attractive platform for topical drug delivery. This system can penetrate through the stratum corneum layer perpendicularly and selectively introduce allergens into the epidermis or dermis for response by antigen-presenting cells in the skin. The final method, namely a nano-based drug delivery system, has been developed as an alternative to overcome skin penetration problems. A variety of nano-assisted drugs, such as lipid nanoparticles, organic-inorganic nanoparticles, dendrimers, and micelles, have been developed for topical and transdermal administration.[29]

Mechanism of Action of EPIT to Achieve Desensitization

In a study using a sensitized mouse model, allergens from EPIT that enter intact skin will be captured in the epidermis by Langerhans cells, which then migrate to the lymph nodes to activate the immune system.[28] In intact skin, administration of EPIT will cause Langerhans cells to activate the immune system. Adaptive by inducing Tregulatory (Treg). Tregs work by inhibiting the activation of T helper 2, which works specifically for allergic responses, thereby reducing the production of IL-4, IL-5, IL-13, and IL-19. Langerhans cells will present antigens to T cells to induce an immune response by Tregs, resulting in inhibition of the allergic response and causing desensitization.[30]

A study in a mouse model of peanut allergy has also proven that Tregs are central to the immune regulatory effects induced by EPIT. Peanut-allergic mice given EPIT injections containing anti-CD25 antibodies (which decrease Tregs) showed increased eosinophilic infiltration. Thus, Treg inhibition would abolish the beneficial effects of EPIT, indicating the critical role of Tregs in inducing desensitization.[31]

The advantage of using EPIT is that allergens are not detected in the systemic circulation.[32] In addition, allergens that enter only pass through the epidermis do not pass through activated keratinocytes (secreting cytokines) or enter the dermis, thereby avoiding sensitization.[28] This advantage is demonstrated in a study using a mouse model with peanut allergy, which showed a decrease in immunoglobulin E (IgE) and an increase in IgG 2a production after administration of EPIT. Epicutaneous immunotherapy also reduces the production of Th2 cytokines by decreasing levels IL-4, IL-5, and IL-13.[32]

Efficacy of EPIT in Peanut Allergy

An open-label study or open trial was conducted on 141 samples aged 4-11 years with an EPIT patch dose of 250 mg peanuts per day, where the therapeutic response was determined by assessing the number of subjects who reached the eliciting dose (ED) or the maximum number of doses before the subject showed subjective symptoms, so therapy must be stopped after 1 and 3 years of treatment. This study showed that 40.4% of subjects achieved ED>1000mg at the 12th month and 51.8% at the 36th month. These results indicate good efficacy of EPIT as there is a statistically significant difference between the 12th and 36th months.[33]

A phase 3 randomized controlled trial was conducted in children aged 1-3 years, which aimed to compare the efficacy of administering a patch containing 250 µg of peanuts to patients with ED ≤ 300 mg for 12 months against a control group that received placebo therapy. Patients are said to have responded well to treatment if the initial ED is >10mg and the ED after therapy is ≥1000mg, or if the initial ED is ≤10mg and the ED after therapy is ≥300mg. This study showed that 67% of children in the intervention group showed a good response to treatment compared to 33.5% in the placebo group.[34]

Another phase 3 RCT study in children aged 4-11 years was conducted by providing an intervention in the form of a patch containing 250µg of nuts for 12 months to assess the response to therapy with ED≥300 mg at baseline ED ≤10mg and ED≥1000mg at baseline ED 10-300mg showed that the therapeutic response in the intervention group (ED baseline ≤10mg and 10-300mg) reached 35.3%, compared 13.6% in the placebo group. Even though the proportion of responders showed statistically significant results, the lower limit of the 95% confidence interval (CI) for the difference in the proportion of the intervention and placebo groups (12.4%) could not equal or exceed the absolute margin of 15%. Therefore, this experiment is said not to show positive results. However, the clinical relevance of these results still requires further study.[35]

Safety of EPIT in Peanut Allergy

Epicutaneous immunotherapy (EPIT) shows potential as a new future treatment for food allergy. The mode of action, which shows that allergens administered via EPIT to the skin do not enter the circulation but instead activate dermal dendritic cells to influence immune activation, is still questionable as to its safety for patients, especially children.[36] A phase 1 clinical trial study was conducted using the Viaskin© patch in 100 subjects (30 of whom were children) by administering doses of Viaskin© 20 mg, 100 mg, 250 mg, and 500 mg applied to the hands with monitoring time 24 hours and 48 hours. During the period of therapy, two types of adverse event reactions were assessed. First, it is called Treatment-Emergent Adverse Events (TEAEs), reactions that did not only occur at the site of the Viaskin© patch. Second, it is Local Treatment-Emergent Adverse Events (L-TEAEs), reactions that happened in the Viaskin© site only. Symptoms of vomiting, eye pruritus, nasal congestion, and throat irritation may indicate TEAE. Meanwhile, the symptoms of L-TEAE can be shown as pruritus, erythema, edema, and urticaria.[37]

In this study, it was found that the TEAE of the participants was mild and temporary, without any significant differences between treatment groups. Meanwhile, the incidence of L-TEAE occurred more in subjects who used Viaskin© with a 48-hour regimen. Safety parameters, including vital signs, general appearance, changes in peak respiratory flow/FEV1, and laboratory parameters,

did not show any changes during the study. This study concluded that the use of EPIT in peanut allergy was declared safe and well tolerated with high compliance from the subjects.[37]

The use of Viaskin© is declared safe for all age groups with recommendations for use from the Data and Safety Monitoring Board (DSMB) as follows:[37]

- Viaskin© 250 mg for children (6-11 years) with non-severe allergy.
- Viaskin© 500 mg for adolescents (12-17 years) with non-severe allergy.
- Viaskin© 500 mg for adults (≥ 18 years) with mild to severe allergy.

Another RCT study in 393 children aged 4-11 years with Viaskin© 250 mg and placebo for 6 months showed that EPIT with VP250 was safe and well tolerated in children with a diagnosis of peanut allergy, both with a high history of anaphylaxis to peanuts or a history of anaphylaxis to other allergic conditions. In this research follow-up, the parents also described the occurrence of TEAE, which was thought to be related to the use of EPIT. The incidence of these TEAEs occurred at a higher rate in subjects receiving VP250 (32%) compared with placebo recipients (14.1%). The TEAE appeared in the form of itching, swelling, and redness with mild to moderate severity and disappears over time. This study concluded that VP250 has good safety as a therapy for children with peanut allergy.[38]

Quality of Life of Peanut Allergy Patients with EPIT

Patients with peanut allergy often experience a decrease in quality of life.[39] Because food is one of the essential things in life, children with food allergies are at risk of causing mild to severe allergic reactions anytime and anywhere.[40–42] With the burden of vigilance and avoidance. This has a detrimental impact on patients of all age groups as well as parents of children with food allergies. This shows that there are consequences of these factors that affect the quality of life of patients with food allergies. Assessment with the Food Allergy Quality of Life Questionnaire (FAQLQ) consistently shows that food allergy has a negative impact on children.[42,43]

Several assessments conducted show that EPIT and OIT can improve the FAQL of children with peanut allergies. A phase 3 clinical trial in children aged 4 to 11 years with EPIT treatment for 12 months of therapy was carried out by assessing quality of life using the Parent Proxy Form Food Allergy Quality of Life Questionnaire (FAQLQ-PF) and Child Form Food Allergy Quality of Life Questionnaire (FAQLQ-CF). The FAQLQ-PF is a proxy report (for example, a parent's impression of a child's FAQL) given to the parents of all subjects aged 12 years and under, while the FAQLQ-CF is completed by children aged 8 to 12 years. This study showed that there was a significant improvement in the total FAQLQ-PF score observed in children after treatment with EPIT compared with placebo.[42]

The change from baseline to month 24 in mean FAQLQ-PF total score was significantly greater in the DBV712 250μg group (one type of Viaskin©) compared with the placebo group (least square/ LS=0.34, P=0.008, where a negative score indicates an increase in FAQL). Significant changes were observed in the subscales of emotional impact (P=0.048), food anxiety (P=0.029), and dietary limitations (P=0.002). Similar improvements in the FAQLQ-CF after EPIT from baseline to month 24 were significantly greater in the DBV712 250μg group compared with the placebo group (LS=0.46; P=0.023, with significant changes observed in the allergen avoidance subscale (P =0.04) and risk of accidental exposure (P=0.002), but not on the emotional impact or dietary restriction subscales. This study suggests that EPIT therapy in peanut allergy can significantly increase FAQL from baseline to the 24th month, both from the child's perspective and the parent's impression of the child.[42]

In comparison, the assessment of PTAH (a biologic drug for oral immunotherapy) for the management of peanut allergy in children appeared to have a beneficial effect on health-related quality of life (HRQoL) using FAQLQ. Improvements were seen despite the rigors of trial participation.[44] While sublingual immunotherapy (SLIT) has proven successful in desensitizing peanut-allergic patients, data on quality of life (QoL) after peanut SLIT is lacking. A study assessed QoL in 28 peanut-allergic children (1-11 years) from a previously published placebo-controlled SLIT trial (22 peanut, 6 placebo). They used a validated food allergy QoL instrument. Subjects were assessed at the start of therapy and one year later at maintenance. In the overall QoL and sub-scores (emotional impact, food anxiety, and social and dietary limitations), there was no difference between subjects on placebo versus peanut.[45]

This literature review provides a comprehensive and up-to-date synthesis of current treatment modalities for peanut allergy, including oral, sublingual, and epicutaneous immunotherapy. The review offers a well-rounded perspective on the efficacy, safety, applicability, and quality of life of each treatment option. The review also identifies important gaps in the literature, offering valuable direction for future research and contributing to a clearer understanding of therapeutic approaches in the management of peanut allergy.

This literature review also has some limitations. Studies included were clinical trials with small sample sizes or short follow-up periods, limiting the generalizability of their findings. Second, this review did not include a formal quality assessment of the studies, which may affect the strength of the conclusions drawn.

CONCLUSION

Epicutaneous immunotherapy opens up new opportunities for developing peanut allergy therapy in children. Regulatory T cells were found to play an essential role in achieving a state of desensitization and reducing allergic response-stimulating cytokines. This EPIT has good efficacy by increasing the eliciting dose and good safety according to the recommended dosage. Apart from that, EPIT can also improve the patient's quality of life. Few clinical trials of EPIT have been conducted in children with peanut allergy. Further research is needed regarding the efficacy, safety, and quality of life of patients after EPIT therapy with a larger sample size and more varied sample characteristics.

ETHICAL CLEARANCE STATEMENT

This study is a literature review and did not involve any human participants, animals, or sensitive data. Therefore, ethical approval was not required.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTION

VF, SSS, and AQN were involved in the conception, design, conduct of the study, and analysis of the data. AY was involved in the conception and supervising of the manuscript. All authors prepare the manuscript and agree for this final version of the manuscript to be submitted to this journal.

ACKNOWLEDGMENTS

We want to give sincere gratitude to all of the people who have supported us: parents, teachers, and friends for always being there and helping us to be the better version of ourselves. We hope that this paper can be beneficial to society.

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