

Therapeutic Application of Honey Against Ige-Mediated Type 1 Hypersensitivity Reactions: A Systematic Review

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ABSTRACT

In contemporary times, the use of traditional remedies is still evident. One of the primary items foremost emphasized today is honey. Aside from its natural sweetener capacity, modern science highlights its potential therapeutic capabilities, including anti-inflammatory and immunoregulatory properties in different Type I Hypersensitivity conditions. This systematic review analyzed nine credible experimental studies to objectify different types of honey and its application and effect in different Type I Hypersensitivity clinical manifestations. The abundance of evidence granting IgE mediated disorders which includes Allergic Asthma, Vernal Keratoconjunctivitis, Allergic Fungal Rhinosinusitis, Allergic Rhinitis, and Atopic Dermatitis in both preclinical and clinical analysis revealed honey to be a contributing factor in suppressing different clinical manifestations of the associated conditions. The systematic review can evaluate and categorize the potential therapeutic capabilities of honey in different IgE-mediated Type I Hypersensitivity Reactions, thus, enabling a comprehended integration towards assisting the application within the clinical setting.

Keywords: Honey, Type I Hypersensitivity Reactions, Chrysin

1 Introduction

The Immune response progresses through a suppressive mechanism that involves the body withdrawing potentially harmful antigens. Occasionally, these antigens can persist in the mechanism, and the immune response induces damage to the body. The reaction can be revealed as Hypersensitivity. Hypersensitivity

reactions can be determined as a normal but an excessive or uncontrolled immune response to an antigen that induces inflammatory reaction, cell death, or tissue injury. There are primarily four classifications for this type of reaction: Types I, II, III, and IV reactions. Reactions that take place due to exposure to an antigen are called Type I hypersensitivity reactions [1]. This type of reaction is commonly known as allergies. The primary immunologic inclusions standard in type I hypersensitivity reactions are mast cells, eosinophils, IgE antibodies, and basophils. Type I hypersensitivity involves two major phases, sensitization, and activation. The body induces an asymptomatic response to the antigen during the sensitization phase, in which the IgE antibody binds to basophils and mast cells that have high-affinity FcεRI receptors. To produce IgE antibodies, isotype switching in B cells is induced by T-helper (Th) type 2 cells and their mediators; in this process, allergen sensitization occurs [2]. Subsequently, during the activation phase, the cross-linking of receptors happens as the allergen attaches to the nearby IgE molecules. Pathophysiology is characterized as allergens presented to T-cells during the sensitization phase. T-cells signal the stimulation of B-cells that are associated with the production of IgE antibodies, which are known to bind to mast cells and basophils' Fc receptors. It emits cell degranulation and triggers the release of certain mediators, which include, proteolytic enzymes, histamine, cytokines, and transcription factors. It permits clinical manifestations which affect one's vascular permeability and smooth muscle contraction that induces an increase in mucous secretions, hypoxia, rhinitis, and bronchospasm [1]. Transcription factors are one of the primary regulators of mast cells that determine allergic responses' susceptibility. One of the primary transcription factors evident in the physiological stimulus of Type I Hypersensitivity and the effect of mast cells is the GATA family. These are compilations of zinc finger proteins known for their ability to recognize and bind the consensus DNA sequence. They commonly have a zinc finger DNA binding domain essential for stabilizing complexes within other proteins [3]. As such, Deng *et al.* [4] cited that the transcription factor, GATA-3, conceals the mast cell activation in an experimental study involving airway rhinitis in mouse models.

In modern times, the availability of natural remedies upholds its potential value in inducing different clinical manifestations. Honey is one of the most natural products viable to provide an alternative therapeutic effect from wound healing to cancer treatment [5]. It primarily consists of different phytochemical components, including many flavonoids and polyphenols such as quercetin, apigenin, kaempferol, and chrysin [6]. Honey's composition varies according to its floral source and origin [7]. For instance, the study also cited that both *Tualang* honey and *Manuka* honey share some similar properties and biochemical characteristics. Given its potential capacity in modern times, a study by Kamaruzaman *et al.* [8] cited that the traditional method of orally administering honey goes directly toward the digestive system; therefore, setting back the efficacy of treating patients that have Type I Hypersensitivity, specifically, asthma. Honey was also reported to have significant anti-inflammatory properties [7]. The study reported that 50 to 80 g of honey ingestion tends to be beneficial and improve the clinical manifestations of allergic rhinitis. In addition to this, the administration of aerosolized honey through inhalation induces a reduced inflammatory cell response.

Honey's progression and its potential therapeutic effect on Type I Hypersensitivity marks a rapid increase in Immunological Research. However, most of these studies are viewed as inconsistent and present contrary statements that permit a dispute among professionals upon verifying the clinical use of these studies. Thus, a systematic review probes a proper evaluation in specific areas that will construe current knowledge and timely information. The purpose of conducting this review is to assess the therapeutic application of the different kinds of honey, against numerous types of Type 1 Hypersensitivity reactions, including, Allergic Asthma, Vernal Keratoconjunctivitis, Allergic Fungal Rhinosinusitis, Allergic Rhinitis, and Atopic Dermatitis, by evaluating existing studies associated with the topic. The review will also deliver considerations between conflicting areas. In addition to this, it will also provide inclusion in both in vivo and in vitro studies that may infuse future assistance in clinical trials.

2 Review Criteria

Sourced from notable databases of journal articles, specifically, PubMed, the articles were extracted by using the keywords, (("Honey"[Mesh]) AND "Hypersensitivity, Immediate"[Mesh]) AND "GATA3 Transcription Factor"[Mesh]). To narrow down the process of selecting the journal articles used in this systematic review, inclusion and exclusion criteria were put into consideration. The inclusion criteria are the following: (1) the diseases or disorders involved should be IgE-mediated hypersensitivities only; (2) the article should also indicate that honey was used for therapeutic reasons; (3) honey should either be taken orally, applied directly to the skin, or ingested through inhalation; (4) the type of honey must originate from *Apis dorsata* and *Apis mellifera* honey bees. On the other hand, when it comes to excluding journal articles, they must satisfy the corresponding criteria: (1) the journal article must not exceed more than ten years; (2) unavailability of abstract; (3) unavailability of full-text; (4) if the article is about honey yet it tackled a different type of hypersensitivity; (5) if the article is about honey but it did not originate from the honey bee species aforementioned. For the selection strategy that we used, we divided our group into four (4) pairs, and, other than the criteria that we have set for our selection process, each pair made use of Covidence, a streamlining medium that aids in screening journal articles that could be used in systematic reviews.

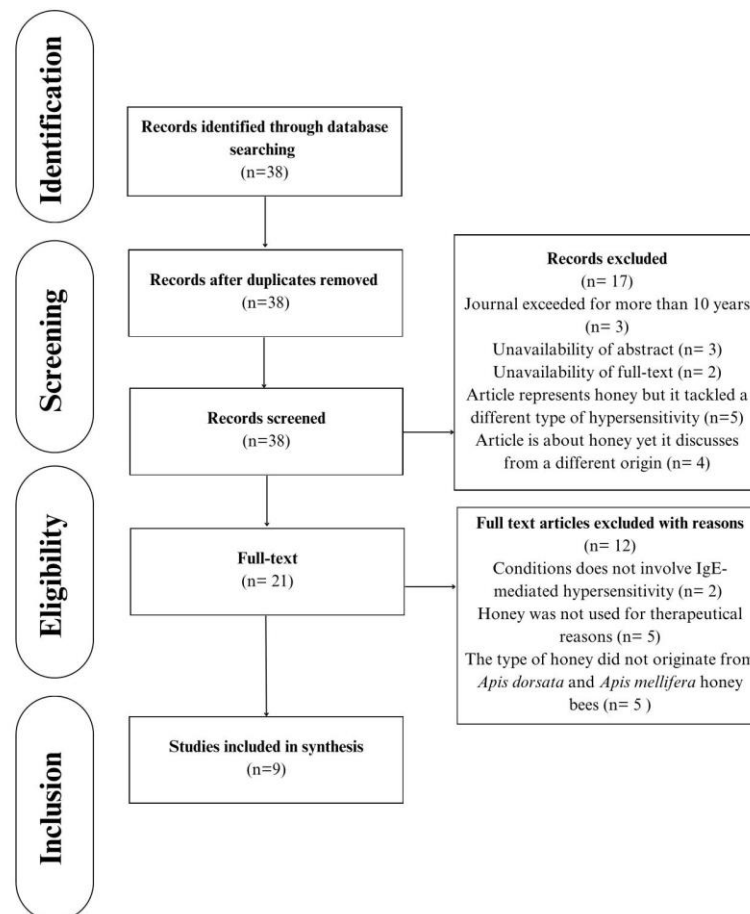


Figure 1: PRISMA flow diagram for systematic review and meta-analyses.

The researchers were able to acquire 38 articles about hypersensitivity, honey, GATA3 Transcription Factor, and IgE-mediated hypersensitivities, and only 9 of these 38 papers were eligible for inclusion; the decisions have been made feasible through the use of Covidence by casting a vote on what must be included (Figure 1). Meta-analysis and research on broader conditions including, asthma, rhinitis, dermatitis, and conjunctivitis were included as long as these hypersensitivities were scrutinized, discussed, and examined

with honey as a treatment. If the articles had been revised and updated by the same authors or research team, only the most recent review was included to obtain the most up-to-date papers. Outdated papers that are older than ten years are excluded to produce more credible review papers. Articles that were not published in English were also rejected because analyzing the research quality of those systematic reviews was complicated.

3 Analysis

3.1 General Characteristics of the Study

Table 1: Summary Characteristics of included studies

Authors, Year	Type of Honey	Treatment Methods	Dose	Type 1 Hypersensitivity	Evaluation	Findings
Alangari, A. <i>et al.</i> , (2017) [9]	Manuka honey	Topical methods	Once/day; 1 week	Atopic Dermatitis	TIS, Enzyme linked immunosorbent assay	There was a significant improvement in the mean of TIS score and no significant changes in the skin staphylococci.
Asha'ari, Z., <i>et al.</i> , (2013) [7]	Tualang honey	Oral ingestion	1g/kg body weight, Once/day; 8 weeks	Allergic Rhinitis	ARIA	There was an improvement in the mean of the total symptoms score
Yasar M., <i>et al.</i> , (2016) [10]	Propolis (a component of honey)	Intranasal and Oral ingestion	200 mg/kg; 3 weeks	Allergic Rhinitis	Symptom assessment, Histological assessment	There were favorable effects of propolis on allergic symptoms and nasal histology
Thamboo, A., <i>et al.</i> , (2011) [11]	Manuka honey	Intranasal	2mL, Twice/day; 4 weeks	Allergic Fungal Rhinosinusitis	Endoscopic grading system	There was no significant improvement from the treatment.
Salehi, A., <i>et al.</i> , (2014) [12]	Topical honey	Eye drop	NI; 4 weeks	Vernal Keratoconjunctivitis	Slit lamp, Limbal papillae, Intraocular pressure, Visual acuity	There was a significant effect in reduction of redness and limbal papillae and improvement.
El-Aidy, W., <i>et al.</i> , (2014) [13]	Apiary honey	Intraperitoneal administration	650 mg/kg, Once/day; 2 weeks and 4 days	Allergic Asthma	Peripheral white blood count, Histopathological examination	There was a significant decrease in Th-1 mediated cells.
Shamshuddin, N., <i>et al.</i> , (2016) [14]	Gelam honey	Oral ingestion	10% (v/v), 40% (v/v) and 80% (v/v); 5 days	Allergic Asthma	Histopathological analysis of lung, Total cell counting, Beta-hexosaminidase assay	There was a significant reduction in the thickening of the airway epithelium, in the number of mast cells and in inflammatory cells. Levels of beta-hexosaminidase were attenuated. However, no significant difference is seen in mucus expression.

Kamaruzaman, N., <i>et al.</i> , (2014) [8]	Tualang honey	Aerosolized	25% (v/v) and 50% (v/v); 2 days	Allergic Asthma	Collection of BAL fluid, Histological and morphometric analyses	There was a significant reduction in inflammatory cells, in thickness of the airway epithelial and mucosal regions, and inhibition of goblet cell hyperplasia and over-production of mucus.
Du, <i>et al.</i> , (2012) [15]	Chrysin, a flavonoid from honey	Intragastric	50 mg/kg, 1 week 3 days	Allergic Asthma	Measurement of airway responsiveness to Ach, BALF, Lung histology, Measurement of T- bet and GATA-3 protein	There was a significant reduction of airway inflammation, and suppression of airway hyperreactivity.

TIS, Three Item Survey; ARIA, Allergic Rhinitis and its Impact on Asthma; NI, Not Indicated; BAL, Bronchoscopy and Bronchoalveolar Lavage; BALF, Bronchoalveolar Lavage Fluid

Out of the 38 acquired studies, this meta-analysis and systematic review included only a total of 9 studies. Seven different types of honey were utilized including Apiary honey, Gelam honey, Topical honey, Tualang honey, Propolis (a component of honey), and Chrysin (a flavonoid from honey). Seven different treatment methods were used in administering these honeys as treatment, inserting as topical application, oral ingestion, intranasal, eye drop, intraperitoneal administration, aerosolized, and intragastric. The sample size in the included studies ranges from 14 to 60 subjects. Both preclinical and clinical investigations were included in the review and the subjects include: patients, Sprague-Dawley rats, con-albumin-induced murine models, OVA-induced BALB/c mice, and OVA-induced rabbit. The Type 1 hypersensitivities included in the study were Atopic Dermatitis, Allergic Rhinitis, Allergic Fungal Rhinosinusitis, Vernal Keratoconjunctivitis, and Allergic asthma. The summary characteristics of the included studies are shown in Table 1.

3.2 Effects of Honey on Atopic Dermatitis

A study by Alangari *et al.* [9] evaluated the effect of Manuka honey (MH) in Atopic Dermatitis by comparing the treated site with MH and the untreated site. Three Item Survey (TIS) and Enzyme-linked immunosorbent assay were used to evaluate the study, which revealed a significant improvement in the mean TIS score. In a dose-dependent manner, MH is also revealed to be effective in suppressing the release of IL4- induced CCL26 from HaCat cells but no effect on IL4-induced IL8 observed at either protein or mRNA levels. MH also exhibited no effect on the skin staphylococci test. Moreover, a one-year follow up interview was done and three patients reported an overall improvement on the treated site even without using Manuka honey after the experiment period. Unfortunately, the researchers could not decipher the active ingredients present in the Manuka honey that caused these findings.

3.3 Effects of Honey on Allergic Rhinitis

It was revealed that a high-dose of Tualang honey, in addition to the prescribed drug (Loratadine), had an additive impact on Allergic Rhinitis [7]. It was revealed that when patients were taking an antihistamine alongside with the honey treatment, there was a significant improvement in the 4 cardinal symptoms such as nasal discharge, nasal obstruction, nasal itching, and sneezing, and the improvement lasted even after the medicine (antihistamine) was stopped, with the exception of rhinorrhea. Honey's pre-clinical study was conducted by Yasar *et al.* [10] which investigated the anti-allergic activity of propolis through both intranasal and oral ingestion in an ovalbumin-induced allergic rhinitis rat model. Oral administration resulted in a significant decrease in inflammation and ciliary loss, as well as an increase in vascular proliferation, goblet

cells, eosinophil count, and symptoms score 1-4 ($p < 0.05$), whereas intranasal administration resulted in a significant decrease in eosinophil count, chondrocytes, vascular congestion, and symptom score 1, 3, and 4 ($p > 0.05$) and no significant difference in ciliary loss, number of goblet cells, inflammation, vascular proliferation, and symptoms score 2 and 5 ($p > 0.05$). Due to this, researchers inferred that the route of oral ingestion (systematic) is better than intranasal use.

3.4 Effects of Honey on Allergic Fungal Rhinosinusitis

The effectiveness of utilizing Manuka honey in patients who proceeded with a bilateral functional endoscopic sinus surgery (FESS), intensive postoperative medical management, and still suffering from Allergic Fungal Rhinosinusitis (AFRS) was investigated in a study by Thamboo *et al.* in 2011 [11]. Out of thirty-four patients with AFRS, nine exhibited a positive response after honey treatment, eight exhibited a worse response and seventeen exhibited no impact. There were no indications of significant differences in the mucosal score and there is no consistent trend in the qualitative analysis of the microbiology results. However, those patients who responded positively to the treatment exhibited high levels of IgE and a general sense of improvement. The researchers suggest that Manuka honey could be suitable only for a certain subtype of AFRS.

Effects of Honey on Vernal Keratoconjunctivitis

Salehi *et al.* [12] conducted a study on Vernal Keratoconjunctivitis patients to evaluate the use of topical honey eye drops as well as its efficacy and safety. Following completion of the study, the eye pressure in the experimental group dramatically increased, although remained within normal limits. The use of honey eye drops reduces eye redness in patients in group 1 when compared to group 2. After the study, there is a significant difference in the experimental group's right eye limbal papillae when compared to the control group, suggesting that the right eye has fully recovered (100%). In comparison to seven individuals in the control group, only one patient in the experimental group developed limbal papillae on the left eye after the study. In conclusion, the number of limbal papillae in the experimental group declined significantly throughout the study.

3.5 Effect of Honey on Allergic Asthma

Back in 2014, El-Aidy, W. *et al.* [13], conducted a study that shows the evaluation of honey on peripheral blood leukocytes (Hematological studies) and lung inflammation (Histopathologic studies) in mouse conalbumin-induced asthma models. In terms of neutrophils, lymphocytes, and monocytes, otherwise known as TH-1 mediator cells, there was a significant reduction in their value. On the contrary, TH-2 mediator cells, eosinophil, and basophil show to have an increased value in the sensitized and honey treated groups compared to the naïve group in the peripheral blood and lung tissue. *Inflammation was scored as 1+ if the inflammatory cells were sporadic, 2+ if perivascular and not more than five layers deep or all-around peribronchial, and 3+ if there were more than five layers with all around inflammation.* Some asthma histological abnormalities were detected as a result of epithelial cell shedding or edema in focal cases of asthma. *Alveoli dilation is a common sign in asthmatics, as the alveoli expand due to airway constriction. In extreme cases of emphysema, the alveoli burst and become confused due to air hyperinflation, an irreversible complication of airway restriction* [13].

A study on forty-two Balb/c mice was conducted to determine the efficacy of Gelam honey in preventing histopathological alterations in the lungs of a mouse model of allergic asthma [14]. In both the OVA and control groups, there was a statistically significant difference in epithelial thickness and inflammatory cell infiltration, showing that airway inflammation had been successfully produced. Group III (40% v/v dose of honey) showed considerable improvement in epithelial thickness, mast cell number, and mucus expression. The administration of 80 percent (v/v) Gelam honey significantly reduced the percentage of airway epithelium stained positively with PAS when compared to the untreated group. The 80 percent (v/v) honey treatment group and the control groups, on the other hand, showed no statistically significant difference in mucus expression. Mast cells in the lungs of mice exposed to OVA were reduced significantly

in honey-treated groups containing 80 percent (v/v) honey. Gelam honey, at concentrations of 40% and 80% (v/v), significantly reduced the number of inflammatory cells in a dose-dependent manner. In conclusion, high concentration Gelam honey reduces histopathological changes in allergic asthma mice model.

Another study was conducted to investigate the effect of aerosolized honey on airway tissues in an ovalbumin (OVA)-induced asthma model in rabbits [8]. The efficacy of honey to act as a rescue agent for asthma symptoms or as a preventive agent for asthma was also investigated. Honey aerosol inhibited inflammatory cell response. Aerosolized honey reduced the concentration of eosinophils in BAL fluid. It was cited that the rescue group had fewer inflammatory cells than the preventative group, and the 50% honey had a better effect. Nonetheless, this study suggests that honey aerosol therapy can lower inflammatory cell responses. Aerosolized honey impacted airway structures by reducing epithelial thickening. Following OVA induction, both rescue and preventative treatments with aerosolized honey repaired the airway structures. Following asthma induction with OVA, honey therapy was found to significantly lower the thickness of the airway epithelial and mucosal areas in all four treatment groups. Honey inhalation, on the other hand, did not significantly improve the condition of the submucosal region. The number of goblet cells decreased in all treatment groups after honey inhalation.

Du, Q. together with his colleagues conducted a study back in 2012. The researchers investigated the effects of chrysin on airway inflammation in a mouse model of allergic asthma, as well as the potential pathways via which it occurs [15]. When comparing the chrysin group to the OVA group, there was a significant reduction in airway resistance after treatment. Chrysin reduces allergic airway inflammation in mice when administered topically. Following therapy with chrysin, the number of total inflammatory cells and eosinophils in BALF was dramatically reduced. When compared to OVA-challenged mice, chrysin greatly reduced the infiltration of eosinophil-rich inflammatory leukocytes in the body. When administered to a mouse asthma model, chrysin reduces airway goblet cell hyperplasia and mucus production. Chrysin affects BALF Th1/Th2 cytokines and serum total IgE. The chrysin group had lower total serum IgE levels than the OVA group. Chrysin affects T-bet and GATA-3 ratio in the lungs. Compared to OVA-sensitized/challenged mice, chrysin treatment raised T-bet and GATA-3 ratio. Chrysin has anti-inflammatory and immunoregulatory capabilities, which shed light on its immunopharmacological significance in an asthma mouse model.

4 Discussion

Pre-clinical and clinical studies provided that honey has signifying effects against IgE-Mediated Type 1 hypersensitivity reactions. Manuka honey permitted a possible treatment for Atopic Dermatitis due to its immunoregulatory effects and anti-staphylococcal properties that may cure skin inflammation [9]. HaCaTs were treated 2 hours earlier with 50 ng/mL IL4 but the analysis of the p-STAT6/STAT6 densitometry ratio failed to present the inhibition of STAT6 phosphorylation and the downregulating mechanism of CCL26 mRNA expression by Manuka honey. The study of Asha'ari *et al.* [7] presented an experiment wherein the case group were given Tualang honey (1g/kg body weight of honey in different doses for 4 weeks) with a daily dose of 10 mg of Loratadine for 4 weeks while the control group were given honey-flavored corn syrup (same dose) as a placebo. Both groups presented an improvement in the symptoms however at week 8, only the case group showed significant improvement in the symptoms which confirms that honey oral ingestion at a large dose in combination with an antihistamine alleviated all four cardinal symptoms of Allergic Rhinitis (AR). As opposed to the study of Yasar *et al.* [10] the anti-allergic activity of Propolis (a honey component) has shown that chondrocytes, vascular congestion, eosinophils, and symptoms scores were all significantly reduced in rats that were given Propolis intranasally, while ciliary loss, inflammation, rise in goblet cells, vascular proliferation, eosinophils, and symptom scores were also significantly reduced in rats that were given Propolis orally. In addition to this, the antimicrobial and antifungal properties of Manuka honey (MH) were examined as a possible treatment in patients with allergic fungal rhinosinusitis (AFRS) [11]. The objective was to reduce the mucosal edema, promote sinus drainage, and eliminate the

infections present but unfortunately, the initial study did not provide much significance in treating AFRS with MH. The Manuka honey may be known for its antimicrobial and anti-inflammatory properties however, the study did not present effectiveness for the treatment of AFRS and thus, in need of further research.

In a clinical study by Salehi *et al.* [12] the use of topical honey eye drops in individuals suffering from vernal keratoconjunctivitis (VKC) was proven effective. Compared to the control group, participants in group 1 who had honey drops had less redness in both their eyes, showing clear improvements from the treatment. Therefore, the findings of this study demonstrated that using honey drops can help reduce redness and limbal papillae while also alleviating VKC. Some studies opposed a contradicting view in which it was cited that Th2-mediator cells (e.g., eosinophil and basophil) exhibit an increased value [13]. Whereas a study provided the use of Gelam honey to inhibit allergic hallmarks of asthma using ovalbumin-induced models, thereby providing a significantly reduced mucus expression in the histopathological characteristics [14]. Concerning this, the study by Kamaruzaman *et al.* [8] signifies honey as a reducing factor in the inflammatory response towards asthma manifestations. Different clinical trials recommended the capability of honey in alleviating histopathological changes in allergic asthma and its capacity to prevent asthma development. With further developments, it was also revealed that several factors like night symptoms, shortness of breath and wheezing were significantly decreased in both groups pertaining to adult asthmatic patients [16]. Abbas *et al.* [17] stated that aerosolized honey permits a rapid absorption towards the airways as it ensures its total deposition. Apart from this, the inclusion of the bioactive ingredient, Chrysin, was studied by Du *et al.* [15] where it cited its effectiveness in allergy-induced airway inflammation in murine models with allergic asthma. It attributed a marked suppression of AHR that influences the restoration of Th1/Th2 imbalance and the reduction of eosinophilic airway inflammation. Rao *et al.* [18] referred honey to have a potential efficacy, depending on the types of phenolic compounds evident.

As discussed in this review, there is evidence to foresee honey as a potential therapeutic agent in suppressing Type 1 Hypersensitivity reactions. However, there is still minimal firm approval on whether honey can alleviate long-term maintenance of hypersensitivity manifestations and using honey alone in managing symptoms. As such, different honey administration routes also prompt immunoregulatory properties, yet these effects may vary. One of the cited studies' primary limitations was honey's uncertainty towards its specific mechanism and functions in different types of allergic diseases. In particular, the bioactive molecules honey acquires are yet to be analyzed in future references.

5 Conclusion

Conclusively, honey can provide general applicability in its therapeutic use in treating Type 1 Hypersensitivity reactions. Different factors should be considered in which the type of honey, application, and route of administration should be taken into consideration. Preclinical and clinical studies consequently affect the different types of Type 1 hypersensitivity reactions, including Atopic Dermatitis, Allergic Rhinitis, Allergic Fungal Rhinosinusitis, Vernal Keratoconjunctivitis, and Allergic Asthma because the effectiveness of honey produces different results per study such as the mechanisms it makes towards the allergic diseases mentioned. Although some studies provided a limited demonstration of honey's specific mechanism, certain studies granted a substantial perception regarding honey's allergic responses. The study suggests that future researchers should primarily focus on the bioactive compound from honey called Chrysin which they can use as a reference on their future studies. As honey primarily contains flavonoids as a phytochemical ingredient, the introduction of Chrysin, which proved its efficacy when it comes on treating asthma with its anti-inflammatory and anti-allergic benefits from this study, marked a progressive hallmark in identifying its potential capacity in inducing allergic manifestations. However, as time progresses, certain limitations may be fulfilled with newer studies, thereby attributing profound information towards honey's potential capacity and its suppressing mechanism towards Type 1 Hypersensitivity reactions.

6 Declarations

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6.2 Competing Interests

The researchers declare that the paper was administered without any financial or commercial relationships that could cause a conflict of interest.

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