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Progress in the understanding of the pathology of allergic asthma and the potential of fruit proanthocyanidins as modulators of airway inflammation

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Allergic asthma is a chronic inflammatory lung disease characterized by sensitization of the airways, and the development of immunoglobulin E antibodies, to benign antigens. The established pathophysiology of asthma includes recurrent lung epithelial inflammation, excessive mucus production, bronchial smooth muscle hyperreactivity, and chronic lung tissue remodeling, resulting in reversible airflow restriction. Immune cells, including eosinophils and the recently characterized type 2 innate lymphoid cells, infiltrate into the lung tissue as part of the inflammatory response in allergic asthma. It is well established that a diet high in fruits and vegetables results in a reduction of the risk of developing inflammatory diseases. Secondary plant metabolites, such as proanthocyanidins which are found in apples, blackcurrants, boysenberries, cranberries, and grapes, have shown promising results in reducing or preventing allergic asthma airway inflammation. Recent evidence has also highlighted the importance of microbiome-mediated metabolism of plant polyphenols in modulating the immune system. In this review, we will discuss advances in our understanding of the pathophysiology of allergic asthma, including the role of the microbiome in lung immune function, and how proanthocyanidins modulate the airway inflammation. We will highlight the potential of dietary proanthocyanidins to impact on allergic asthma and the immune system.

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1. Introduction

Our historic understanding of the pathology of asthma has progressed from it being a collection of symptoms dominated by a restricted airflow but with little knowledge of the underlying causes^{1,2} to recognizing it as an inflammatory lung disease,^{3,4} initially subtyped as either allergic or non-allergic asthma. We have progressed beyond asthma being defined as a single disease with two simple subtypes,⁵ as clinicians seek to better understand asthma diagnosis and treatment through clustering patients by phenotype,⁶ clinical presentation, and the underlying pathophysiological molecular mechanisms.^{6,7} Advances in our understanding of immune function in asthma such as the identification of the innate lymphoid cells (ILCs),^{8,9} increased understanding of the functions of T-helper 2 (Th2) cells and IgE adaptive immunology,¹⁰ as well as recent progress in the role of the human microbiome in disease^{11,12}

have contributed to this shift towards classifying asthma as multiple endotypes.^{5,7}

Proanthocyanidins are polyphenol compounds which belong to the flavonoid class of plant secondary metabolites.¹³ Proanthocyanidins are oligomeric in structure, built from flavan-3-ol monomeric units, catechin and epicatechin, and their gallated derivatives.¹⁴ These monomeric units can be linked together through the A-type or B-type linkage, and the number of linked monomers is referred to as the degree of polymerization (DP), with 2–10 DP being typical. The sub-classification of proanthocyanidins can be reduced further, such as when referring to the structurally defined dimeric compounds procyanidin A2 or procyanidin B2.^{14,15} Fruits, particularly apples, blackcurrants, boysenberries, cranberries and grapes, are the most common, though not the most concentrated, dietary source of proanthocyanidins,¹⁶ with chocolates, tea and wine also all having high concentrations of proanthocyanidins. Proanthocyanidin bioactivity beyond the lung, and inflammation, has been reviewed elsewhere.^{13,17–24}

This review will focus on the recent progress in our understanding of the pathology of eosinophilic allergic asthma²⁵ and highlight the potential of dietary proanthocyanidins to influence disease development or progression. Specifically, we

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will examine the role of ILC type 2 (ILC2) cells in controlling the fate of eosinophils in allergic asthma and explore the role the microbiome has on the progression of allergic asthma, and as an avenue for therapeutic intervention.

2. Pathology of allergic asthma

The established pathology of both allergic and non-allergic asthma involves repeated inflammatory exacerbations of the lung epithelium,²⁶ bronchial smooth muscle hyperreactivity,⁴ mucous production,²⁷ and lung tissue remodeling, resulting in reversible airway obstruction. Allergic asthma was traditionally characterized as an eosinophilic airway disorder perpetuated by overactive Th2 cells, and the overproduction of type-2 pro-inflammatory cytokines, interleukin (IL)-4, IL-5 and IL-13, in response to inhaled allergens. Other T helper-cell subtypes, including Th9, Th17, as well as T regulatory (Treg) cells, have also been implicated in inappropriate airway inflammation.^{28,29}

2.1 The lung epithelium and eosinophilia

The airway epithelium is one of the key regulators of allergic asthma pathology.³⁰ Allergen exposure initiates the release of key cytokines, IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), by epithelial cells. IL-33 induces multiple immune cells, including Th2 cells, basophils, mast cells, and ILC2 cells, to secrete IL-4, IL-5 and IL-13.^{31,32} IL-25 mediates eosinophilic inflammation including airway hyperresponsiveness, airway remodeling, goblet cell hyperplasia, subepithelial collagen deposition, and angiogenesis in a Th2 cytokine-dependent manner.^{33,34} Epithelial TSLP induces OX40 ligand expression in lung tissue-resident dendritic cells, resulting in

priming naïve CD4⁺T cells toward a Th2 phenotype in lymph nodes.^{35,36}

Lung epithelial exposure to allergens also stimulates the release of eotaxins, a family of chemotactic signaling proteins which mediate eosinophil cell infiltration into inflamed tissue. Eotaxins are a family of cc-chemokine proteins with three members: CCL11 (eotaxin-1), CCL24 (eotaxin-2) and CCL26 (eotaxin-3). Eotaxins recruit eosinophil cells into the epithelium, where the eosinophils secrete cationic peptides and reactive oxygen species, causing epithelial injury.^{37–39} Eotaxins also mediate the release of IL-4 stores from within the eosinophil granules.⁴⁰ The expression of each isoform is cell specific with CCL11 being secreted by epithelial cells as well as eosinophils, macrophages, lymphocytes, fibroblasts, and smooth muscle endothelial cells.⁴¹ CCL24 and CCL26 are functional homologues that are primarily secreted by epithelial and endothelial cells.⁴² CCL11 transcription is controlled by both the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 6 (STAT6),⁴³ and is the initial eotaxin isoform produced, whereas CCL26 is predominantly controlled by STAT6 and is the late-stage eotaxin remaining present up to 24 h after allergen exposure.^{43,44} All three eotaxins bind to the eosinophil CCR3 receptor to attract them to the site of inflammation.⁴¹

Eosinophils, like other hematopoietic immune cells, are formed in the bone marrow and migrate into the blood, where they are a small, but stable, population.⁴⁵ Eosinophils are responsible for numerous inflammatory processes during parasitic helminth, bacterial and viral infections, tissue injury, tumor immunology, and allergic disease.⁴⁶ ILC2s (see section 2.2) are a key source of IL-5 required for mediating eosinophil development and survival.^{5,47} During allergic airway inflammatory exacerbations, excess eosinophils in the lung cause damage to the epithelium through the release of cationic pep-



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tides such as eosinophil-derived neurotoxins, and peroxidases.⁴⁵ In a clinical setting, eosinophilia has been demonstrated as a reliable biomarker for the allergic asthma endotype, which is useful for determining the appropriate treatment.⁴⁸ Blood eosinophilia can be consistently quantified through serum IL-5 and IL-13 concentrations.⁴⁹ Peripheral blood ILC2s were also demonstrated to be an accurate biomarker of eosinophilic airway inflammation.⁵⁰ The role of eosinophils across different asthma endotypes has recently been reviewed.⁴⁵

In addition to eosinophil infiltration of lung tissue, other immune cells also play a role in allergic asthma initiation and progression. Macrophages are critical for the development of IL-13-driven tissue inflammation and fibrosis by recruiting T-cells, which actively maintain the tissue-localized immune responses.⁵¹ Additionally, alternatively activated macrophages have been associated with airway disease.^{52–54} Basophil populations have been implicated as a bridge between the commensal-bacterial populations (see section 3.1) and allergic inflammation because the use of antibiotics increases serum IgE concentrations, whereas the depletion of basophil populations reduces the exaggerated immune responses.⁵⁵ Dendritic cells are integral in the crosstalk between the innate and adaptive immunity, and involved in the induction of asthma through antigen sampling across the airway epithelium.³⁵ The involvement of IgE antibodies to benign antigens, and the roles of mast cells and B-cells in allergic asthma have been discussed elsewhere.^{56–58}

2.2 Type 2 innate lymphoid cells

Innate lymphoid cells are a recently characterized family of effector lymphoid cells that protect against pathogens, and restore the tissue integrity.⁵⁹ Three subsets have been characterized based on function, development, and cytokine production: type 1 ILCs produce type-1 cytokines (IFN γ and TNF); type 2 ILCs secrete type-2 cytokines (IL-4, IL-5, IL-9, and IL-13); and type 3 ILCs produce IL-22, IL-17, and granulocyte-macrophage colony-stimulating factor (GM-CSF).⁵⁹ During homeostasis, ILC2s and ILC3s are the predominant subsets that promote immune regulation, and control tissue homeostasis and repair. The functional identity of ILCs is dependent on the cytokines IL-12 and IL-4, and imbalances towards IL-4 result in type 2 pro-inflammatory pathology that has been associated with asthma.⁵⁹ Eosinophil cell survival in peripheral tissues requires IL-5, and the IL-5 concentration is maintained by ILC2 cells.^{47,60,61} ILCs act as innate immune cells correlated with T cells.⁶² It has been suggested that while Th2 cells are the main source of type-2 pro-inflammatory cytokines for atopic, IgE-mediated, eosinophilic asthma, ILC2 cells are the main source in non-atopic eosinophilic asthma, as ILC2 cells are non-antigen specific.¹⁰ The shared roles of ILCs and T cells have been reviewed.⁶² In a BALB/c mouse model of allergic airway inflammation, T-cell derived IL-4/IL-13 was essential for IgE production, recruitment of eosinophils and basophils to the lung, goblet cell hyperplasia, and the development of airway hyperreactivity, whereas ILC2s were recruited to

the lung in the same efficiency in wild-type and IL-4/IL-13 T-cell-specific knockout mice.⁶³ In patients with severe eosinophilic non-atopic asthma, ILC2s are thought to be the predominant source of type-2 cytokines,⁶⁴ although there is also evidence that basophils and mast cells, rather than ILCs, are the cellular source of type-2 cytokines in chronic asthma.³¹

3. Asthma, the microbiome, and dietary intervention

The prominent role of the microbiome in human health has become clear over the last decade.^{12,65–68} There is an association between the reduced diversity in the intestinal microbiome and allergic disease,⁶⁹ as well as evidence that the use of antibiotics increases susceptibility to allergic airway inflammation.⁷⁰ It has also been shown that asthmatics are more likely to have a diet high in saturated fats and cholesterol and low in fiber, fruits, and vegetables, which may promote inflammation and contribute to the perpetuation of asthma pathophysiological features.^{71–73} Adherence to a Mediterranean-style diet, which is high in fiber, fruits, vegetables and fish, is associated with increased fecal short-chain fatty acid concentrations and *Prevotella* and *Lachnospira* genera,⁷⁴ and has been correlated with a reduction in asthma symptoms in children⁷⁵ (Fig. 1).

3.1 The gut and lung microbiome

The risk of developing allergic asthma is determined early in life, with one of the underlying causes being a disruption of microbial communities resulting in airway inflammation.⁷⁶ Epidemiological evidence has suggested a reduced risk of allergic asthma from early childhood exposure to farm environments, barn-microbes, and unpasteurized milk early in life.⁷⁷ However, viral infections and changes in bacterial abundance in the lower airways increase susceptibility to respiratory illness, with early life changes to host-microbiome interactions leading to long-term predisposition to airway inflammation.^{69,78,79} The microbiome is engaged in a complex, bilat-

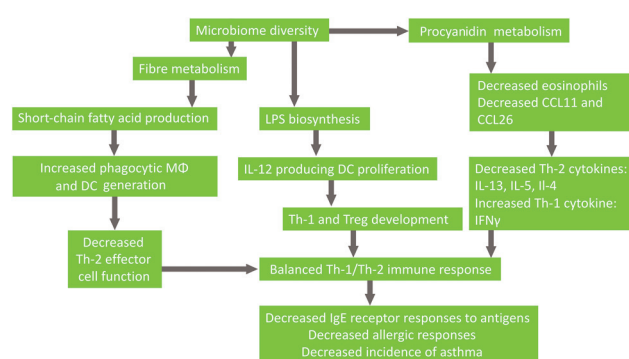


Fig. 1 Flow diagram mapping the interactions between procyanidins, the microbiome and the immune system that impact on allergy and asthma development.

eral interaction with the host, and has a demonstrated effect on the innate immune system.⁶⁷ There is a cross-talk between different mucosal sites which can be demonstrated by the development of Treg cells in the gut following oral probiotics which then migrate to the lung to protect against allergic airway inflammation.⁸⁰

The intestinal microbiome is a potential target for preventing the development of childhood asthma.⁸¹ There is evidence that reduced microbiome diversity in infants is associated with increased allergic sensitization, rhinitis, and blood eosinophilia at the age of 6 years.⁶⁹ Gut microbiome community composition analysis in 3-month-old infants showed that atopic, wheezing subjects, who had a high risk of developing childhood asthma, had a lower abundance of four specific genera: *Faecalibacterium*, *Lachnospira*, *Veillonella*, and *Rothia* (FLVR), with an accompanying reduction in fecal acetate production compared with age-matched controls, although the overall taxa diversity was not different between the groups.⁸¹ There is also evidence that a lower abundance of *Ruminococcaceae*, and a reduction in Actinobacteria diversity, is associated with increased IgE-associated eczema.⁸² Offspring of germ-free mice inoculated with feces from an atopic wheezing subject supplemented with the missing FLVR genera were protected from ovalbumin (OVA)-induced airway inflammation compared to mice inoculated with feces from an atopic wheezing subject without supplemented FLVR.⁸¹ The authors suggested that the reduction in a Gram-negative species (*Veillonella*) may not allow for adequate LPS biosynthesis. LPS induces IL-12-producing dendritic cell proliferation,⁸³ and promotes the development of the Th1 arm of the immune response, providing opposition to Th2 mechanisms (Fig. 1).

The lower airways of the lung were once thought of as sterile, but have been revealed as a host of commensal bacteria and an important component in the overall human body microbiome. It is typical of infants to be initially colonized with *Staphylococcus* or *Corynebacterium* before stable colonization with *Alloiococcus* or *Moraxella*.⁸⁴ The interactions between the host and the airway microbiome train the maturing infant immune system for tolerance through a cycling process involving Th2 cells and Treg cells and require programmed death ligand 1 (PD-L1);⁸⁵ however, viral infections, antibiotic use, and daycare attendance can interfere with this development and result in airway mucosal dendritic cells with increased expression of the high-affinity IgE receptor leading to a greater allergic response.^{69,76,79}

3.2 Dietary intervention to modify the microbiome

Evidence supporting dietary intervention that modifies the gut microbiome to improve health is growing.⁷⁴ High-fiber diets yield a distinct acetate-producing gut microbiome profile in pregnant mice, which protected the offspring from developing allergic airway disease through increased *in utero* acetate exposure;⁸⁶ conversely, low Bacteroidetes diversity in mothers pre-birth contributed to infants developing IgE-associated eczema.⁸² Berry fruit is a rich dietary source of soluble fiber, and, as previously mentioned, it is also a common source of

proanthocyanidins.^{16,87,88} Fruit consumption satisfies two of the three 'P's for gut health: probiotics, prebiotics, and polyphenols.⁶⁶ The interaction between polyphenols and the gut microbiome related to human health has been reviewed.^{65,68,89–94}

The biological effects of the proanthocyanidin consumption are clear despite the studies showing minimal absorption of radio-labeled proanthocyanidins with 88–94% being recovered from the gastrointestinal tract or the feces.⁹⁵ The gut microbiome has been suggested as the missing link between the poorly absorbed proanthocyanidins and improved health outcomes as a result of their consumption.⁹⁵ Consuming fruit-derived polyphenols to modulate the immune system has been demonstrated in the models of metabolic syndrome, where Concord grape polyphenol extract,⁹⁵ blackcurrants and blueberries improved health outcomes that were modulated *via* the gut microbiome. The consensus is that smaller microbiome-produced metabolites are responsible for much of the health-promoting activities of proanthocyanidins. An *in vitro* fermentation model, which was used to investigate the metabolism of procyanidins by the human fecal microbiome, indicated that catechin, epicatechin, procyanidin B2, procyanidin A2, and partially purified apple procyanidins, as well as partially purified cranberry procyanidins can all be metabolized by human fecal bacteria.⁹⁶ Comparatively, A-type linked and high-DP compounds were more resistant to microbial catabolism than B-type linked and low-degree of polymerization compounds.⁹⁶ Both procyanidin A2 and partially purified cranberry extracts show at least 50% original compounds after 24 h of fermentation. Further supporting this, lingonberry supplementation, a fruit high in A-type linked proanthocyanidins, has been shown to prevent low-grade inflammation in high-fat diet fed mice through increasing the relative abundance of *Akkermansia* and *Faecalibacterium*, two genera associated with anti-inflammatory activity and a healthy gut.⁹⁷ Deciphering the interplay between the gut microbiome and dietary components will allow for advancements in personalized nutrition.⁹⁸ The modulation of the lung microbiome by dietary intervention and/or polyphenols is still in its infancy and requires further research.

3.3 Proanthocyanidin inhibition of eosinophilia biomarkers

Proanthocyanidins evolved in plants as an environmental stress-response, such as towards UV damage and drought, and are biologically active in the context of human health.^{16,99,100} Many plant-derived food polyphenols have been investigated for their ability to attenuate allergic airway inflammation,¹⁰¹ with a recent investigation on the proanthocyanidins' role in inhibiting eosinophilia, a hallmark feature of allergic asthma. Eosinophil cell infiltration of the lungs can be predicted in humans most reliably with serum measurements of IL-13 and IL-5, as well as CCL26.⁴⁹ Various blackcurrant cultivar extracts, specifically proanthocyanidin-enriched blackcurrant extracts, were shown to inhibit the *in vitro* production of CCL26 in type-2 cytokine-stimulated human alveolar epithelial cells.^{101,102} Apple extracts have also been shown to inhibit the human

Table 1 Summary of proanthocyanidin-containing fruits and their effects on allergic airway inflammation

	Source	Structure	Model	Biomarkers	Citations
Apple		B-type proanthocyanidins Procyanidins B1 and B2	Lung epithelial <i>in vitro</i>	↓CCL11, ↓CCL26	103
Blackcurrant		B-type proanthocyanidins Procyanidins B3 and B4	Lung epithelial <i>in vitro</i> , mouse <i>in vivo</i>	↓CCL11, ↓CCL26	101, 102 and 104
Boysenberry		B-type proanthocyanidins Procyanidin B4	Mouse <i>in vivo</i>	↓iNOS, ↑arginase ↑pro-fibrolytic alternatively activated MΦ	110
Cranberry		A-type proanthocyanidins Procyanidin A2	Lung epithelial <i>in vitro</i>	↓CCL11, ↓CCL26	105 and 106
Grape (and grape seeds)		B-type proanthocyanidins Procyanidin B1	Lung epithelial <i>in vitro</i> , mouse <i>in vivo</i>	↓IL-4, ↓IL-13 ↓IL-5 ↓lung eosinophil count ↓Lung tissue remodeling ↓Fibrosis ↑IFNγ	107–109

alveolar epithelial cell production of CCL11 and CCL26 *in vitro*, and the inhibition of CCL11 correlated with increased proanthocyanidin compounds in the extracts.¹⁰³ *In vivo*, blackcurrant extracts can inhibit eosinophilia through the reduced production of CCL11 in an OVA-induced allergic airway inflammation mouse model.¹⁰⁴ Similarly, procyanidin A2 inhibits both CCL11 and CCL26 in type-2 cytokine-stimulated human alveolar epithelial cells.^{105,106} A summary of different proanthocyanidin-containing fruits and their effects on allergic airway inflammation can be found in Table 1.

A commercially purchased proanthocyanidin-rich grape seed extract was shown to ameliorate a comprehensive set of biomarkers for inflammation, bronchial hyper responsiveness, and lung tissue fibrosis in both acute and chronic murine models of allergic asthma.^{107–109} Grape seed proanthocyanidin extracts typically consist of B-linked proanthocyanidins, although no specific chemistry was given in these studies. The Th2 cytokines IL-13 and IL-5 were reduced, while the Th1 cytokine IFNγ was increased, suggesting that grape seed extract supported the rebalancing of the Th1/Th2 antagonistic relationship¹⁰⁷ (Fig. 1). BALB/c mice chronically challenged with OVA for eight weeks that were treated with grape seed extract had a reduced eosinophil count, and decreased IL-4 and IL-13 in BALF, as well as reduced tissue remodeling and fibrosis compared with controls.^{108,109} Additionally, boysenberry extracts can also reduce lung tissue fibrosis by supporting the development of pro-fibrolytic alternatively activated macrophages in a chronic model of allergic airway inflammation.¹¹⁰

The data from *in vitro* cell, and murine *in vivo*, studies are promising; however, few human trials have been conducted to investigate a proanthocyanidin supplement or food preparation. Although there is not yet a clear protocol for a proanthocyanidin-based therapeutic intervention, there is epidemiological evidence in humans that clearly demonstrates that proanthocyanidin exposure is advantageous for

health and results in a decreased risk of inflammatory disease.^{111–114}

A novel, future approach for investigating the proanthocyanidin inhibition of airway inflammation could be the direct application of structurally defined polyphenolic compounds to the lung *via* inhalation. A recent study used A-type procyanidins in a preparation administered intranasally to a mouse model of allergic rhinitis, which has Th2-dominated pathology similar to asthma.¹¹⁵ Investigating proanthocyanidins administered through inhalation would complement oral ingestion by possibly allowing biologically active parent compound structures access to pulmonary target tissue while also gaining benefit from the complex mixtures of metabolites generated by the microbiome.

4. Concluding remarks

Understanding the therapeutic benefit of fruit proanthocyanidins still remains a challenge with respect to dietary consumption, because of the low bioavailability of parent compounds, the complexity of the resulting metabolites of the microbiome, and their ability to gain access to or influence tissues outside the gastrointestinal tract. It is imperative for research in this area to progress for investigators to clearly identify biologically active polyphenolic moieties within a fruit extract. *In vitro* work must consider the physiological relevance of the investigated doses and compounds, and *in vivo* work should monitor the microbiome profiles. Additionally, human trials should use appropriate biomarkers for measuring allergic asthma outcomes. As our understanding of chronic inflammatory diseases, including allergic asthma, continues to progress, we can continue to characterize the use of foods and structurally defined proanthocyanidin compounds for therapeutic interventions to support tissue-specific and overall health.

Conflicts of interest

The authors declare no conflict of interest.

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