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Soluble fibre as a treatment for inflammation in asthma

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HIGHLIGHTS

- Asthma is a highly prevalent chronic respiratory disease driven by inflammation.
- Reduced dietary fibre intake is associated with increased systemic inflammation.
- Metabolites generated by soluble fibre fermentation have anti-inflammatory effects.
- Preclinical evidence suggests a role of soluble fibre in reducing inflammation in asthma.
- Emerging clinical research suggests a role for soluble fibre in targeting inflammation in asthma.

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ABSTRACT

Asthma is a highly prevalent inflammatory disease of the airways. Bacterial metabolites of soluble fibre fermentation, such as short chain fatty acids (SCFAs), have been shown to exert anti-inflammatory effects via free fatty acid receptor activation and epigenetic regulation through inhibition of histone deacetylases (HDACs). The aim of the present review was to summarise the available evidence for soluble fibre in the treatment and prevention asthma. There is substantial preclinical evidence suggesting soluble fibre may be beneficial in the airways. The clinical evidence in this area is limited, however available studies to date have reported promising evidence for the future of soluble fibre interventions as an adjunct treatment in asthma management.

1. Introduction

Dietary fibre is an important component of a healthy diet, contributing to satiation and healthy bowel movements. There are many types of dietary fibres with numerous structural differences, including complexity and incorporated monosaccharide units. However, the basic structure of dietary fibre consists of monosaccharide units bound together by β-(1, 4) linkages, which are resistant to digestion by mammalian enzymes [32]. The most widely accepted method of fibre classification is based on solubility in water at a fixed pH and/or fermentability[111]. Thus, dietary fibre can be referred to as water-insoluble and poorly fermented or water-soluble and well fermented. Research suggests that dietary fibre, particularly soluble fibre, also confers health benefits via metabolites synthesised upon fermentation within the gastrointestinal tract by resident commensal bacteria.

Diet quality and fibre consumption has significantly decreased in affluent nations, resulting from the increased consumption of readily accessible processed foods [1]. A report from the Australian Bureau of Statistics found that less than 4% of the Australian population reached minimum vegetable and legume recommendations, and only 30% consumed the recommended serves of grains. In parallel, Western nations have an increased prevalence of non-communicable diseases including obesity, type 2 diabetes, cardiovascular disease and some cancers [2–5], whose aetiologies involve inflammatory processes. Therefore, the increased consumption of soluble fibre may potentially be important in mitigating the inflammatory processes underlying chronic conditions leading to the improvement of disease status.

Asthma is a chronic inflammatory disease, which has a high clinical prevalence in Westernised countries including Australia (14.7%), Canada (14.1%) and the US (10.9%) [6]. Primarily a disease of the conducting airways, asthma is associated with abnormal airway physiology and airway remodelling. Alterations to the structure of the airways include airway smooth muscle hyperplasia, thickening of the basement membrane, goblet cell metaplasia and mucus hypersecretion, and epithelial changes including epithelial fragility and cilia dysfunction [7,8]. Asthma often involves inappropriate responses to innocuous antigens in the airways, with disease pathogenesis and exacerbation driven by airway inflammation in response to allergens and infection

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[11]. Soluble fibre is an emerging anti-inflammatory treatment which may be relevant in asthma [12]. The metabolites of bacterial soluble fibre fermentations are thought to act via mechanisms which reduce inflammation and improve tolerogenic immune responses, including free fatty acid receptor activation, upregulation of regulatory genes (e.g. *Foxp3*), and regulation of immune cell chemotaxis via activation of mitogen-activated protein kinase (MAPK) pathways. The aim of the present review is to summarise the available evidence surrounding the anti-inflammatory mechanisms of soluble fibre in the context of asthma.

2. Epidemiology of fibre, prebiotics and inflammation

Dietary fibre has a number of health benefits. It promotes regular laxation and there is strong evidence that intake is associated with a reduced risk of a range of chronic diseases including cardiovascular disease [13], type 2 diabetes [14] and colorectal cancer [15]. The protective effects of fibre may extend to other conditions, as a recent meta-analysis found that consumption of an additional 10g of fibre each day is associated with an 11% reduction in all-cause mortality [16]. However, worldwide fibre intake is well below recommended intake levels. In Australia, adults consume an average of 21g fibre each day, with more than 80% failing to meet the Suggested Dietary Target (SDT) for reducing chronic disease risk (28g for women and 38g for men) [17]. Intakes are similar across Europe and the United States [18].

Systemic inflammation is implicated in the pathogenesis and/or severity of many chronic diseases including cardiovascular disease [19], type 2 diabetes [20], chronic kidney disease [21] and asthma [22]. An inverse association between dietary fibre intake and systemic inflammation has been observed [23–25], and it has been suggested that dietary fibre reduces chronic disease risk by mediating inflammatory processes. In a recent systematic review, 8 out of 11 (73%) randomised controlled trials (RCTs) supplementing adults with an oligosaccharide prebiotic reported a reduction in at least one inflammatory biomarker, such as C-reactive protein (CRP) or tumour necrosis factor (TNF) compared to the maltodextrin-supplemented control group [26]. One out of 2 studies (50%) found that supplementing preterm infants with an oligosaccharide blend reduced serum TNF, interferon (IFN)-γ and interleukin (IL)-1β. It is likely the negative study was confounded by the fact that it recruited infants with acute diarrhoea, as acute infection elevates systemic inflammation in response to infection [27]. However, only 3 out of 12 (25%) RCTs supplementing adults with a polysaccharide prebiotic supplement reported a reduction in at least one inflammatory biomarker. The lack of evidence found supporting polysaccharide supplementation to reduce systemic inflammation likely falls with the fermentability of the supplement provided.

Numerous epidemiological studies have demonstrated associations between dietary fibre, systemic inflammation and disease risk or severity. For example, Ning et al. [28] found that a higher dietary fibre intake lowers the risk of developing cardiovascular disease (CVD) and is associated with a significantly lower CRP in 11,113 adults aged 20–79 years. Within this population, a higher fibre intake was associated with lower blood pressure, cholesterol, insulin and body mass index (BMI) [28]. In adults with chronic kidney disease, increasing fibre intake by 10g was associated with a 38% reduced odds of having an elevated CRP [29]. Dietary fibre intake was inversely associated with mortality in this population [29]. Qi et al. [30] found that a low intake of cereal fibre was associated with significantly higher CRP and TNF-receptor 2 (TNF-R2) in women with diabetes. In relation to risk of developing diabetes, a low dietary fibre intake (≤20 g/day) increased the risk of developing diabetes in older men [relative risk, RR -1.47 (1.03–2.11)] [31]. Fibre intake was inversely associated with CRP and IL-6 levels in these men [31]. Interestingly, adjusting for systemic inflammation attenuated the association between fibre intake and diabetes risk [RR 1.28 (0.88–1.86)] [31], suggesting that inflammation is driving this association. Adults with severe asthma have been shown to have a significantly (5 g/day) lower dietary fibre intake compared with adults without asthma [24]. In adults with asthma, fibre intake is inversely associated with eosinophilic airway inflammation and lung function [24]. There is therefore some evidence from epidemiological studies that fibre is associated with reduced systemic inflammation and reduced chronic disease risk. Intervention studies are required to provide further evidence of this association.

3. The role of the microbiome in SCFA synthesis

The gut microbiome is a dynamic environment, consisting of commensal bacteria which exist in a synbiotic relationship with the host, and pathogenic bacteria, which when present in sufficient numbers may cause disease. Intestinal bacteria present as the limiting factor in SCFA synthesis from prebiotics. Dietary fibre resists breakdown through the β-configuration of bonds which exist between monomers, as intestinal digestive enzymes are specific to α-configurations [32]. Dietary fibre includes both insoluble and soluble forms, such as non-starch polysaccharides (e.g. cellulose), resistant oligosaccharides (e.g. galactooligosaccharide, inulin-like fructans), resistant starches (e.g. pectin), and lignin. The primary physiological role of insoluble fibre is to absorb water for faecal softening and bowel movement regularity, whereas soluble fibre aids in slowing the gastric emptying process to facilitate satiety.

Soluble fibre has also emerged to have a prebiotic effect on the microbial ecosystem within the gastrointestinal tract [32]. Soluble fibre undergoes heterotrophic metabolism by anaerobic bacteria present in the colon, leading to the production of many metabolic by-products, such as SCFAs and lactate (Fig. 1). SCFAs include free fatty acids containing less than 6 carbon atoms, such as acetate, propionate, and butyrate (Fig. 1) [33]. The production of SFCA in the gastrointestinal tract is both dependent upon, and has the capacity to alter, the composition of the host colonic microbiota. Bacteria from genera such as *Bifidobacteria* and *Lactobacilli* ferment soluble fibre to produce SCFA (Fig. 1). SCFAs lower luminal pH, preferentially stimulating the growth of these

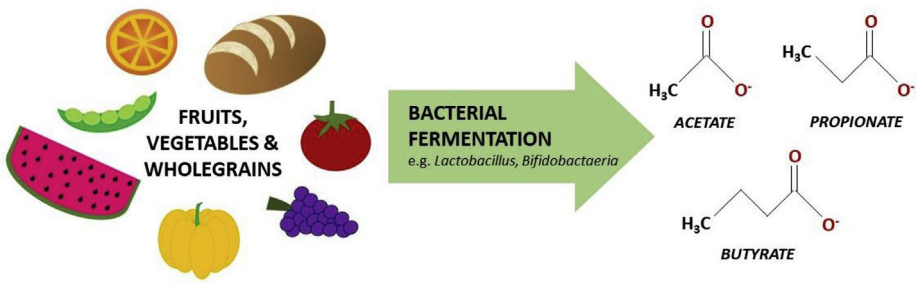

Fig. 1. *Short chain fatty acid synthesis*. Soluble fibre from the diet is fermented by bacteria resident within the gastrointestinal tract to produce metabolites including short chain fatty acids acetate, propionate and butyrate.

classically "health-promoting" bacteria and inhibiting the growth of "harmful" bacteria, including enteric pathogen *Escherichia coli* [34]. A number of studies have demonstrated postprandial SCFAs are generated following a soluble fibre meal [35–39], and that these SCFAs are a result of bacterial fermentation [40,41]. The generation of SCFAs by commensal bacteria creates a microbial cross-feeding dynamic where the by-product of one species metabolism provides substrate for another bacterial species [42]. Furthermore, the capacity for fibre intake to modulate the composition of microbiota has been described in a recent systematic review [43]. Accepted prebiotic fibres, including inulin and human milk oligosaccharides, significantly increased *Bifidobacteria* (mean difference 0.68, 95% C.I. 0.38–0.98) and *Lactobacillus* (mean difference 0.34, 95% C.I. 0.13–0.55) abundances compared to placebo [43].

Carlson et al. used an *in vitro* fermentation system to assess the fermentability of different fibres and the ability of SCFAs to alter colonic bacteria [44]. Xylooligosaccharides (XOS) were found to be the greatest producers of acetate, while propionate and butyrate synthesis were greatest with a fibre containing 28% β-glucan and inulin, respectively. Inulin and a chicory root blend significantly elevated *Collinsella* bacteria, while XOS was the only fibre which significantly increased the *Bifidobacteria* population. XOS, inulin, pure β-glucan and a 28% β-glucan blend reduced Firmicutes numbers. Inulin and XOS were the only fibre blends which increased beneficial bacteria populations while simultaneously reducing pathogenic bacteria. Interventions looking to use soluble fibre as an anti-inflammatory treatment should implement an oligosaccharide supplement rather than polysaccharide or resistant starch for greatest effect.

4. Immunomodulatory mechanisms of SCFAs

4.1. Activation of free fatty acid receptors

Asthma pathogenesis and severity is linked with pro-inflammatory mechanisms. Furthermore, systemic inflammation has been associated with and increased exacerbation risk [45,46], increased airway inflammation [47,48], and poorer lung function [46,47,49,50] in asthma sufferers. Soluble fibre may ameliorate these effects by exerting anti-inflammatory action via SCFAs binding to associated G-protein coupled receptors (GPCRs). SCFAs bind free fatty acid receptors GPR43, GPR41 and GPR109a in a dose-dependent manner [51]. These receptors regulate the activity of second messengers cyclic adenosine monophosphate (cAMP), or inositol triphosphate (IP_3) and diacyglycerol (DAG) depending upon the G-protein α subunit. GPR41 is widely expressed is human tissues and coupled to Gαi, whereas GPR43 is expressed primarily on immune cells and is coupled to both Gαi and Gαq [51–53]. Gαi coupling inhibits adenylyl cyclase activity, leading to reduced cAMP accumulation and thus protein kinase A (PKA) activation (Fig. 2). Inhibition of the cAMP pathway through GPR41/43 may be important in altering the NF-κB activity, due to the role PKA plays in phosphorylation and activation of NF-κB subunits, including p50 (NF-κB1) and p65 (RelA), at serine residues (Fig. 2) [54]. Gαq coupling increases phospholipase C activity, leading to the generation of IP_3 and DAG. IP_3 increases intracellular calcium $[Ca^{2+}]_I$, while DAG leads to the activation of protein kinase C and the synthesis of arachidonic acid (AA) (Fig. 2). AA synthesis is important as AA is metabolised by lipoxygenase and cyclooxygenase (COX) enzymes into prostaglandins, thromboxanes and leukotrienes, which go on to mediate inflammatory responses [55].

GPR43 has been shown to interact with βArr2, leading to up-regulation of IκBα, the inhibitor of NF-κB, which is an important transcription factor in the genesis of inflammation [56,57]. Inhibition of NF-κB activation and binding in turn leads to reduced expression of inflammatory cytokines, including tumour necrosis factor (TNF), interleukin-1β (IL-1β) and IL-6 (Fig. 2). Butyrate has been shown to act as agonist for GPR109a, another orphan GPCR [58]. GPR109a is highly expressed in adipose tissue and on various immune cells, and is coupled to Gαi [59–61]. However, while both GPR41 and GPR109a are both coupled to Gαi subunit, only GPR109a has been found to interact with the βArr2 pathway like GPR43, and therefore has the capacity to reduce NF-κB inflammatory gene expression [62]. GPCRs also have the ability to activate MAPK pathways through downstream GPCR signaling or via arrestin binding and endocytosis of the receptor-arrestin complex [63]. Activation of GPR41 and GPR43 by propionate and acetate, respectively, is coupled to the activation of ERK1/2, JNK1-3 and p38 [64]. The MAPK signaling cascade is an essential pathway controlling many biological and physiological functions including cell proliferation, apoptosis and inflammation. The activation of these pathways has previously shown to be important in guiding the immune response [65], including immune cell chemotaxis and degranulation [66–68].

4.2. Epigenetic regulation

Alterations to gene expression in the absence of changes to the DNA sequence is termed epigenetic regulation. Epigenetic modifications include DNA methylation and histone modifications, often occurring as a result of environmental stimuli, altering the accessibility of genes through changes in chromatin density, thus regulating expression patterns. Histone acetylation is an important epigenetic mechanism by which gene expression is regulated [69]. Hyperacetylation causes an increase in gene expression, whereas hypoacetylation leads to reduced gene expression. Gene expression and suppression via acetylation is regulated by two classes of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs) [70]. HATs are enzymes responsible for the acetylation of histone proteins, reducing the attraction between histone proteins and the DNA, thus facilitating access of transcriptional machinery (Fig. 3), such as RNA polymerase II, holoenzyme and transcription factors, to the DNA template [70]. HDACs are enzymes which restore this polarity through the removal of acetyl moieties from histone proteins, reinstating the "closed" or Heterochromatin structure (Fig. 3).

It is well described that immune tolerance mechanisms are impaired in asthma. Therefore, it can be hypothesised that restoration of tolerogenic and anti-inflammatory gene expression, through epigenetic mechanisms, may serve as means for asthma prevention and management. SCFAs, butyrate and propionate, are known epigenetic regulators which function by inhibiting HDAC activity (Fig. 3). HDAC proteins are classified into two families: NAD^+-dependent HDACs and classical Zn^{2+}-dependent HDACs [71]. The latter HDAC family consists of class I (including HDAC1-3, and 8), class IIa (HDAC4, 5 7, and 9), class IIb (HDAC6 and 10) and class IV (HDAC11) HDACs. The former family of HDACs, referred to as sirtuins (SIRTs), consist of class III HDACs which include SIRT1-7 [72]. HDAC inhibition by SCFAs is primarily carried out by butyrate and propionate, which enter the cell via passive diffusion or through sodium-coupled monocarboxylate transporters (Slc5a8), on class I and IIa HDACs (Fig. 3) [73,74]. It is unclear whether acetate has HDAC inhibitory capability. However, one study, supplementing mice within a model of allergic airways disease (AAD), found acetate treatment increased acetylation at the FOXP3 promotor region suggesting potential epigenetic capacity [75].

It is important to highlight that the acetylation and deacetylation process elicited by HATs and HDACs, respectively, is not limited to changes in chromatin density [76,77]. These enzymes have the capacity to modify non-histone proteins, including transcription factors and nuclear receptors, through post-translational modifications. For example, NF-κB activity is regulated by localisation and association with its inhibitor, NF-κB inhibitor alpha (IκBα). Acetylation of IκBα at lysine residue 221 (K221) impairs the association between NF-κB and IκBα, increasing NF-κB DNA-binding and transcriptional activity [78]. HDAC3 deacetylates IκBα, facilitating increased association between NF-κB and IκBα, thereby reducing NF-κB-mediated gene expression [79]. Further research should investigate the impact of HDAC inhibition by SCFA in terms of cytosolic protein activity.

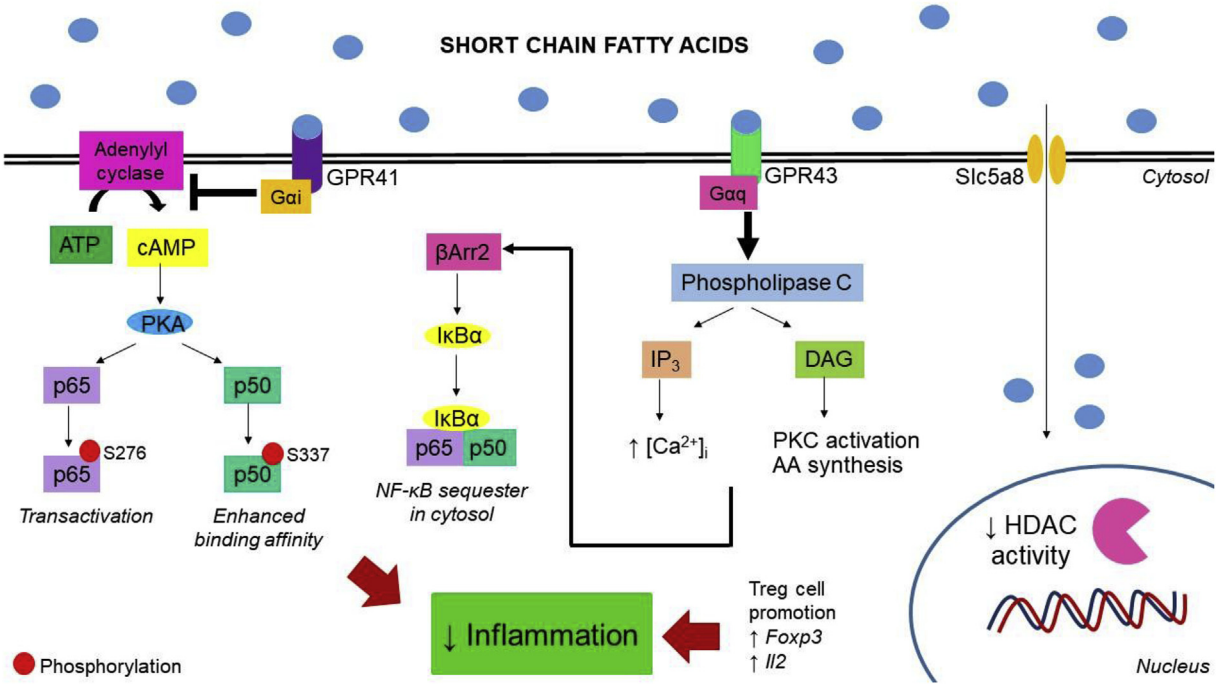

Fig. 2. *Anti-inflammatory mechanisms of SCFAs.* Short chain fatty acids activate G-protein-coupled receptors and inhibit histone deacetylases (HDACs) to execute anti-inflammatory processes. Activation of GPR41 inhibits adenylyl cyclase activity through the inhibitory G protein α subunit (Gαi) leading to a reduction in second messenger cyclic adenosine monophosphate (cAMP) accumulation and protein kinase A (PKA) activity. Active PKA would causes phosphorylation and activation of canonical nuclear factor-kappa B (NF-κB) subunits, NF-κB1 (p50) and RelA (p65) at serine residues 337 (S337) and 276 (S276), respectively, enhancing transcriptional activity. Inhibition of this pathway by GPR41 stimulation reduces the synthesis of inflammatory cytokines. GPR43 stimulation increases phospholipase C activity through Gαq, increasing second messengers inositol triphosphate (IP_3) and diacyl glycerol (DAG). IP_3 increases intracellular calcium ($[Ca^{2+}]$), and DAG increases protein kinase C (PKC) activity and arachidonic acid (AA) synthesis. GPR43 recruits β-arrestin 2 (βArr2) through a negative feedback loop. βArr2 recruits IκBα, enhancing sequester of NF-κB in the cytosol and inhibiting NF-κB nuclear translocation. Short chain fatty acids may enter the cell passively or through sodium-coupled monocarboxylate transporter Slc5a8, where they go on to inhibit histone deacetylase (HDAC) activity, altering chromatin density and gene expression.

5. *In vitro* and *in vivo* use of SCFAs and prebiotics for inflammation

Preclinical studies have evaluated the use of prebiotics and synbiotics prophylactically, and in the treatment of, models of allergic airways disease (AAD) (Table 1). Galacto- (GOS) and fructooligosaccharides (FOS), and bacteria from the *Bifidobacterium* genus are the most frequently reported prebiotics and probiotics used during supplementation, respectively. Overall, studies which have looked at models of allergic disease have shown prebiotic and synbiotic supplementation inhibits T_H2 immune response development to allergens, reduces eosinophilic inflammation, and increases regulatory T lymphocyte activity in animal models of allergic inflammation (Table 2).

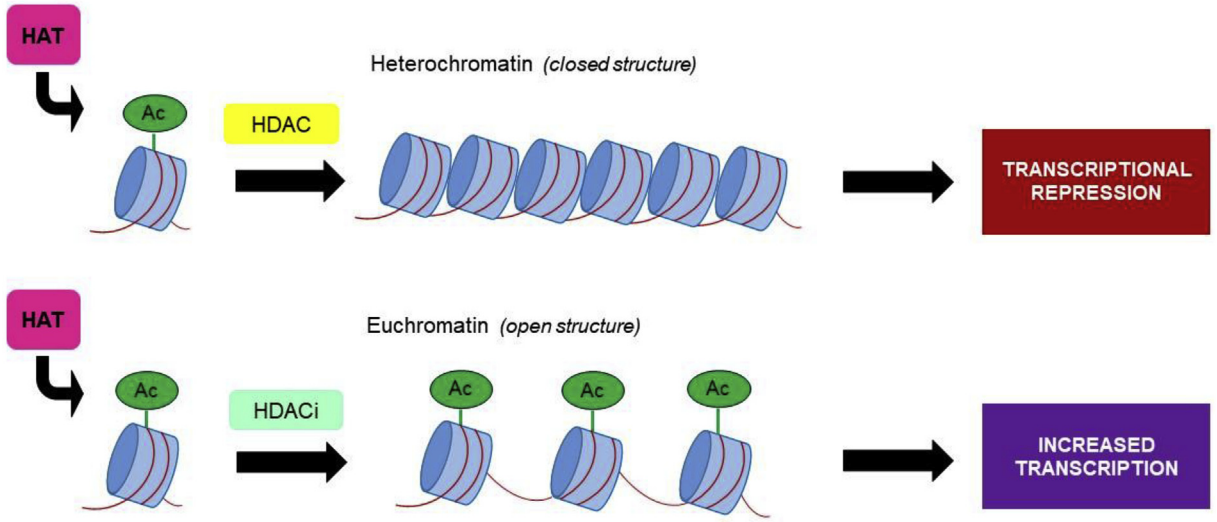

Fig. 3. *Acetylation as an epigenetic mechanism.* Histone acetyltransferases (HATs) add acetyl moieties to histone proteins, reducing the attraction between histones and DNA resulting in a more "open" chromatin structure (Euchromatin) facilitating transcription. Histone deacetylases (HDACs) remove acetyl groups and encourage a "closed" chromatin structure (Heterochromatin) which is less transcriptionally active. HDAC inhibitors (HDACi) inhibit the removal process of acetyl groups, allowing more transcriptional activity.

Table 1
Effects of short chain fatty acids on immune cell responses to endotoxin *in vitro*.

Cell type	SCFA(s)	[SCFA]	Effect	Reference
Human mDCs	C3	1 mM	↓ *CXCL9, CXCL10, CXCL11, Il6, Il1b* ↓ IL-6, IL-12p40	[82]
	C4		↓ *CXCL9, Il6* ↓ IL-6, IL-12p40	
Human PBMCs	C2/C3/C4 combined	2 mM	↓ IL-1β, IL-2, IL-6, IL-17, IL-12 ↑ T_{reg}:T_H17 cell ratio	[83]
Human PBMCs[a]	C2 C3 C4	2 mM	↓ IL-4, IFN-γ, TNF, IL-12, TGF-β1 ↑ IL-10 (↔ acetate) ↑ PBMC Treg population	[84]
Human PBMCs[a]	C2 C3 C4	20 mM	↓ IL-10, MCP-1, TNF, IFN-γ ↔ IL-1β, IL-2, IL-6, IL-8, IL-12p40	[85]
Human monocytes[a]	C2 C3 C4	20 mM	↓ IL-10, MCP-1 ↔ IL-1β, IL-2, IL-6, IL-8, IL-12p40, IFN-γ, TNF	

C2, acetate; C3, propionate; C4, butyrate; CXCL, chemokine (C-X-C motif) ligand; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; mDC, myeloid dendritic cell; PBMC, peripheral blood mononuclear cell; TNF, tumour necrosis factor; Treg, regulatory T cell.

[a] Note: effect comparable across all SCFA unless otherwise noted.

C57BL/6 mice on a low fibre diet (< 0.3% dietary fibre) sensitised to house dust mite (HDM) demonstrated increased inflammatory cell infiltration into the lungs upon challenge, dominated by eosinophils and lymphocytes, compared to mice fed a standard 4% fibre diet [80]. Mice fed a low fibre diet also demonstrated increased concentrations of T_H2 cytokines, including IL-4, IL5, IL-13, as well as the T_H17 cytokine, IL-17A, in lung tissue homogenates compared to control mice [80]. In contrast, mice exposed to either a high fibre diet or oral propionate treatment demonstrated reduced T_H2 cytokines in the lungs and reduced goblet cell hyperplasia and mucus production [80]. This mimics findings from previous studies (Table 2), and suggests that a low fibre diet increases susceptibility to asthma development whereas a high fibre diet is protective.

Up-regulation of regulatory T cell-specific genes, particularly *Foxp3*, is the most commonly reported mechanism by which prebiotics and probiotics may be modulating allergy development and allergic immune responses. One study found that HDAC9−/− mice were protected against the development of AAD [75]. Similarly, in humans, HDAC9 has previously been associated with asthma severity [81]. Furthermore, it has been shown that mice conditionally deficient in HDAC11 in T_{reg} cells demonstrated increased immune regulatory function, coupled with an increase in *Foxp3* and transforming growth factor-β (TGF-β) expression. Therefore, HDAC inhibition may be an important target in asthma prevention and treatment. Whilst the majority of *in vivo* evidence concerns epigenetic mechanisms, it has previously been shown that GPR41-deficient mice administered propionate developed similar airway eosinophilia to saline-treated mice in a model of AAD, while GPR43-deficient mice maintained a reduced inflammatory response to HDM following propionate treatment. This suggests immunomodulatory mechanisms can also occur through GPCR-dependent pathways, and that the mechanisms relevant in asthma protection may be GPR41-dependent [80].

The majority of *in vitro* work has examined the effects of direct SCFA treatment on inflammatory responses of immune cells to lipopolysaccharide (LPS) (Table 1). Peripheral blood mononuclear cells (PBMCs) are the primary human cell type which has been exposed to SCFAs directly [31–33]. Despite varying concentrations of SCFAs in both combined and separate forms, there is a distinct anti-inflammatory effect (Table 1) [82–85]. Two out of 3 studies measuring IL-6 production in response to LPS demonstrated reduced IL-6 release with SCFA treatment (Table 1) [82,83]. Similarly, 3 out of 4 studies measuring IL-12 demonstrated a reduction in IL-12 response to LPS following SCFA treatment (Table 1) [82–84]. Despite the anti-inflammatory effect demonstrated, LPS stimulation occurs through toll-like receptor 4 (TLR4) signaling [86], and thus is not indicative of how SCFAs affect the immune response to other stimuli. Interestingly, it has been shown that acetate and propionate promote the differentiation of naïve T cells into T_H1 effector cells in the presence of T_H1 conditions (IL-12, IL-2 and anti-IL-4), resulting in upregulation of T-bet and IFN-γ mRNA [87]. Similarly, these SCFAs have been reported to induce differentiation into T_H17 effector T cells in the presence of a T_H17 environment (IL-1β, IL-6, IL-21, IL-23, TGF-β and anti-IFN-γ), causing upregulation of mRNA encoding IL-17A, IL-17F, RoRα and RoRγt [87]. These data suggest that SCFA may have the ability to promote appropriate immune responses. However, future research should investigate this hypothesis in models of viral and bacterial infections.

6. Clinical evidence for the use of prebiotics in asthma during different life stages

6.1. In utero

Exposure to bacterial metabolites *in utero* is hypothesised to alter neonatal development through epigenetic programming [75]. A number of epidemiological studies have found associations between maternal diet and the risk of asthma development in offspring, with a recent systematic review revealing reduced risk of wheeze in offspring was associated with maternal vitamin D (OR 0.58, 95% C.I. 0.38–0.88), vitamin E (OR 0.54, 95% C.I. 0.41–0.71) and zinc (OR 0.57, 95% C.I. 0.40–0.81) intakes [95]. Dietary fibre is often not a reported component of these studies and thus its evaluation has been limited to the consumption of high fibre foods, such as fruits and vegetables. However, meta-analysis revealed no associations between maternal fruit (OR 1.03, 95% C.I. 0.81–1.31) and vegetable (OR 0.90, 95% C.I. 0.69–1.18) intake with risk of wheeze in offspring [96–99]. In addition, there were no associations between maternal fruit (OR 1.03, 95% C.I. 0.81–1.31) and vegetable (HR 0.97, 95% C.I. 0.60–1.58) intake with the risk of asthma development in offspring [95,99,100]. It is difficult to assess the impact of maternal dietary fibre on asthma development in offspring as available data is limited to foods which act as partial markers of fibre intake. Interestingly, higher maternal serum acetate concentrations during late stage pregnancy have previously been associated with a reduced percentage of infants requiring GP visits for symptoms of cough and wheeze, and reduced parent-reported symptoms of wheeze in the first 12 months of life [75]. However, this association was not found in offspring from mothers with asthma.

6.2. Pregnancy

Evidence for dietary interventions to improve asthma control during pregnancy is very limited. It has previously been reported that following adjustment for maternal age, maternal BMI, smoking status, socioeconomic status, parity and ethnicity, a preconception maternal diet high in fat, sugar and takeaway food was associated with uncontrolled asthma (aOR 1.54, 95% CI 1.07–2.23) [101]. In contrast, there were no associations found between asthma control status and other preconception dietary patterns [101]. Further research is needed to assess the role of maternal fibre intake in asthma management during pregnancy, and to determine whether improved maternal asthma control through nutrition impacts respiratory outcomes in offspring.

6.3. Infants

It is proposed that early life exposures are critical to the

Table 2
Preclinical studies assessing the impact of fibre, prebiotics and synbiotics in models of allergic airways disease.

Animal(s)	Sensitisation	Intervention	Control	Outcome	Reference
Brown Norway rats	Aerosol OVA	Prebiotic diet (50 g/kg raffinose)	Control diet (0g raffinose)	↓ BALF total leukocytes and eosinophils ↓ IL-4 and IL-5 mRNA expression in lungs ↓ n° mucus-producing cells ↑ bifidogenesis Ø OVA-specific plasma IgE, IgG_1 or IgG_2 Ø IFN-γ mRNA expression in lungs	[88]
Male BALB/c mice	Aerosol OVA	Synbiotic diet (2×10^9 CFU *B. breve* M-16V; probiotic/scFOS, lcFOS and pectin-derived acidic-oligosaccharide (AOS); prebiotic)	Control diet (PBS)	↓ total BALF leukocytes and relative eosinophils ↓ down-regulation of T*lr3*, *Tlr9* and *Nod1* lung expression ↓ *Il1β*, Il6, *Il12*, and *Tnf* ↓ number of collagenous connective tissue fibres in lung ↑ *Il10* and *Il23* ↑ *Foxp3* expression in lungs and blood T_{reg} cells ↑ *Foxp3/Rorγt* and *Foxp3/Gata3* ratios	[89]
Female C57BL/6 and BALB/C mice	Intranasal HDM	High fibre (SF11-025; resistant starch) diet	Control diet (872310)	↓ total BALF leukocytes, eosinophils, macrophages and lymphocytes ↓ MLN T-cell produced IL-4, -5, -13, −10 and IFN-γ ↓ goblet cell hyperplasia ↓ airway hyper-responsiveness ↑ airway compliance	[75]
Female BALB/c and male C57BL/6	OVA	Maternal prebiotic diet (scGOS/lcFOS)	AIN93G diet	↓ OVA-induced AHR ↑ OVA-specific IgG_{2a} ↑ T_{reg} cells	[90]
Male BALB/c mice	Aerosol OVA + AlumInject (adjuvant)	1–1% w/w 9:1 scGOS: lcFOS 2–1% w/w 83% scGOS/lcFOS + 17% pAOS)	AIN93G diet	↓ OVA-induced AHR ↓ OVA-induced BALF inflammatory cells ↓ OVA-specific IgE (ns)	[91]
Male C3H/HeN mice	Intratracheal HDM	Prebiotic diet (2.5% FOS)	Control diet (0% FOS)	↓ BALF eosinophils ↓ goblet cell hyperplasia ↓ IL-5 and eotaxins (ns) ↓ HDM-specific IgG_1 (s) and IgE (ns)	[92]
BALB/c mice	Intranasal HDM (w/Budesonide (500 μg/kg) on day 7, 9, 11, and 13)	Prebiotic diet (1% GOS)	Control diet (0% GOS)	**GOS:** ↓ AHR development ↓ BALF eosinophils **GOS/Budesonide:** ↓ BALF leukocytes ↓ HDM-induced lung CCL5 and IL-13	[93]
Female BALB/c mice	Aerosol OVA	Standard chow (4% fibre) + soluble pectin/ insoluble cellulose	Low-fibre chow (1.75% fibre)	↓ frequency of allergic symptoms (nasal rubbing, sneezing) ↓ BALF and NALF total cells and eosinophils (greater with soluble fibre addition than insoluble fibre) ↓ eosinophilic inflammation and goblet cell metaplasia in nasal mucosa and lung ↓ serum OVA-specific IgE (greater reduction with soluble fibre compared to insoluble) ↓ IL-4 in NALF/BALF ↑ IFN-γ and IL-10 in NALF/BALF ↑ Bifidogenesis	[94]

AHR, airway hyperresponsiveness; BALF, bronchoalveolar lavage fluid; CCL, chemokine CC ligand; CD23, Fc epsilon RII (C-type lectin); CFU, colony forming unit; CT, cholera toxin; DC, dendritic cell; DHA, docosahexaenoic acid; FOS, fructooligosaccharide; FOXP3, forkhead box P3; GATA3, GATA binding protein 3; GOS, galactooligosaccharide; HDM, house dust mite; IFN-γ, interferon-gamma; Ig, immunoglobulin; IL, interleukin; lc, long chain; MLN, mesenteric lymph node; mMCP-1, mucosal mast cell protease-1; MyD88, myeloid differentiation primary response 88; NALF, nasal lavage fluid; NOD-1, nucleotide-binding oligomerisation domain containing 1; ns; not statistically significant; OVA, ovalbumin; pAOS, pectin-derived acidic oligosaccharides; PBS, phosphate buffered saline; PUFA, polyunsaturated fatty acids; RORγt, retinoid-associated receptor (RAR)-related orphan receptor gamma; sc, short chain; SCFA, short chain fatty acid; TGF-β, transforming growth factor-beta; TLR, toll-like receptor; TNF, tumour necrosis factor.

development of allergic disease, with diet presenting as an important factor. Due to the hypothesised immunomodulatory capacity of soluble fibre, supplementation of infants with prebiotics has been suggested for prevention of allergy development. A recent systematic review and meta-analysis revealed a reduced risk of asthma development (RR 0.37, 95% C.I. 0.17–0.80) in infants receiving prebiotics compared to no prebiotics [102]. However, the quality of this evidence was very low. One randomised controlled trial (RCT) found that healthy term infants supplemented with 0.8 g/100 mL oligosaccharides during the first 6 months had a reduced risk of developing persistent wheeze (RR 0.37,

95% C.I. 0.14–0.96) compared to their counterparts fed 0.8 g/100 mL maltodextrin (MDX) [103]. Another RCT reported a reduced incidence of symptoms of respiratory allergy (RR 0.37, 95% C.I. 0.10–1.35) in healthy term infants fed a formula with 8 g/L oligosaccharide-supplemented formula for ≥2 months [104]. However, oligosaccharides alone were not as effective at reducing respiratory allergic manifestations as breastfeeding [104]. Despite this, the addition of an oligosaccharide prebiotic presents a supplementary immune-stimulating ingredient to standard formula preparations in instances where breastfeeding is not a feasible option.

6.4. Children and adolescents

Few clinical trials have evaluated the use of prebiotic supplementation in children and adolescents. One RCT randomised 56 obese and overweight adolescents with poorly controlled asthma to either a twice daily nutrient bar containing 7.84g of dietary fibre (15.68 g/day) or control for 2 months [105]. However, despite improvements in questionnaire-based measures of asthma control and quality of life in both nutrient bar and control groups, there was no difference between intervention and control regarding asthma control or lung function [105]. It is important to note that the study product contained many other nutrients, and thus was not prebiotic specific. More research is needed to evaluate soluble fibre in the treatment of asthma in children and adolescents.

6.5. Adulthood

Clinical evidence for the use of soluble fibre supplementation in patients with asthma predominantly exists in the adult population. The first clinical trial assessing soluble fibre in asthma randomised 29 patients with asthma to a synbiotic (8 g/day oligosaccharide blend: 90% GOS, 10% FOS with probiotic: *Bifidobacterium breve* M − 16V) or placebo for 4 weeks [106]. Following treatment 4 week synbiotic treatment, there was no improvement in HDM-induced bronchial inflammation compared to before treatment. However, this study did find that synbiotic supplementation resulted in a significant improvement in peak expiratory flow (PEF) and reduction in serum T_H2 cytokines. Williams et al. was the first study to use a prebiotic only supplement in patients with asthma [107]. In a crossover design, 10 participants with asthma and 8 controls were randomised to 5.5 g/day of Bimuno-galactooligosaccharide (B-GOS) or placebo for 3 weeks. Following 3 week B-GOS supplementation, peak falls in forced expiratory volume in 1 s (FEV_1) and PEF after voluntary hyperpnoea was reduced by 40% and 11%, respectively in the asthma group only. Furthermore, serum TNF and CRP concentration were significantly reduced in asthma following prebiotic supplementation.

Interestingly, a recent pilot study examined the effects of an acute soluble fibre challenge on patients with asthma [108]. Four hours after 3.5g inulin combined with probiotic yoghurt (*Lactobacillus acidophilis* LA5, *Lactobacillus rhamnosus* GG, and *Bifidobacterium lactis* Bb12), there was a reduction in airway inflammation compared to baseline and an increase in lung function compared to control. Furthermore, this study found GPR41 and GPR43 expression was significantly up-regulated following the intervention, suggestive that mechanisms associated with SCFA-mediated free fatty acid receptor activation may be associated with anti-inflammatory action in the airways of patients with asthma. This was further examined in a 7-day inulin trial, where 17 participants with asthma were randomised in a 3-way crossover design to 12 g/day inulin, 12 g/day inulin + prebiotic, and placebo [109]. Following supplementation with 12 g/day inulin, there was an improvement in asthma control questionnaire (ACQ) score, a reduction in sputum % eosinophils and an increase in faecal *Anaerostipes* bacteria, a genus of considered SCFA-producing bacterium [110]. Furthermore, plasma SCFA concentration demonstrated a moderate positive correlation with FEV_1 [109]. These studies suggest soluble fibre supplementation may be a feasible intervention in the treatment of inflammation in asthma, and highlight an important area for future research.

7. Conclusion

Asthma is an inflammatory disease of the airways which has a high prevalence in westernised countries, where diet quality is increasingly poor due to the preferred consumption of processed foods. This review demonstrates supplementation with soluble fibre presents as a potential adjunct therapy for not only the management of asthma, but its prevention. Further clinical research is needed to fully evaluate the effect of soluble fibre supplementation and dietary fibre intake on asthma prevention and treatment.

List of abbreviations

AA	arachidonic acid
AAD	allergic airways disease
ACQ	asthma control questionnaire
AHR	airway hyperresponsiveness
aOR	adjusted odds ratio
BALF	bronchoalveolar lavage fluid
βArr2	Beta arrestin 2
B-GOS	Bimuno-galactooligosaccharide
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CCL	chemokine CC ligand
CD23	Fc epsilon RII (C-type lectin)
CFU	colony forming unit
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CRP	C-reactive protein
CT	cholera toxin
CVD	cardiovascular disease
CXCL	chemokine (C-X-C motif) ligand
DAG	diacyl glycerol
DC	dendritic cell
DHA	docosahexaenoic acid
ERK	extracellular signal-regulated kinases
FEV_1	forced expiratory volume in 1 s
FOS	fructooligosaccharide
FOXP3	forkhead box P3
GATA3	GATA binding protein 3
GOS	galactooligosaccharide
GPCR	G protein-coupled receptor
HAT	histone acetyltransferase
HDAC	histone deacetylase
HDM	house dust mite
HR	hazard ratio
IFN	interferon
Ig	immunoglobulin
Iκβα	inhibitor of nuclear factor-kappaB
IL	interleukin
lc	long chain
IP_3	inositol triphosphate
JNK	c-Jun N-terminal kinase
MAPK	mitogen activated protein kinase
MDX	maltodextrin
MLN	mesenteric lymph node
mMCP-1	mucosal mast cell protease-1
MyD88	myeloid differentiation primary response 88
NALF	nasal lavage fluid
NF-κB	nuclear factor-kappaB
NOD-1	nucleotide-binding oligomerisation domain containing 1
OR	Odds ratio

OVA	ovalbumin
pAOS	pectin-derived acidic oligosaccharides
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PEF	peak expiratory flow
PKA	protein kinase A
PKC	protein kinase C
PUFA	polyunsaturated fatty acids
RCT	randomised controlled trial
RORγt	retinoid-associated receptor (RAR)-related orphan receptor gamma
RR	risk ratio
sc	short chain
SCFA	short chain fatty acid
SIRT	sirtuins
TGF	transforming growth factor
TLR	toll-like receptor
TNF	tumour necrosis factor
XOS	xylooligosaccharide.

Availability of data and material

Not applicable.

Consent for publication

The authors confirm that the content of the manuscript have not been published, or submitted for publication elsewhere.

Ethics approval and consent to participate

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Author statement

L.M.W, H.A.S and L.G.W conceived the design of this review. L.M.W wrote the introduction, the role of the microbiome in SCFA synthesis, immunomodulatory role of SCFAs, *in vitro* and *in vivo* use of SCFAs and prebiotics for inflammation, clinical evidence for the use of prebiotics in asthma during different life stages, and conclusion. H.A.S wrote epidemiology of fibre, prebiotics and inflammation. L.G.W reviewed and edited the article. All the authors have approved the final version of the manuscript.

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