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REVIEW ARTICLE

The Effect of Dietary Fiber on Asthma Through Cytokine Production

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ABSTRACT: Asthma is a chronic disease that harms both adults and children, causing symptoms such as debilitating shortness of breath, wheezing, coughing, and in severe cases, even death. There is no cure for asthma, only therapies that can help control asthma symptoms. One significant, under-examined possibility for a supplement to these therapies is dietary fiber. Dietary fiber, found in various everyday foods including grains, fruits, and vegetables, can maintain gut health and a balanced gut micro-biome, which improves the body's immune system and overall health. This paper will review evidence for the relationships between asthma and dietary fiber - specifically how dietary fiber could be used as a supplementary therapy. One of the byproducts of the fermentation of dietary fiber are short-chain fatty acids (SCFAs). One significant function of SCFAs is that they can regulate the production of cytokines. This review paper will examine the benefits of dietary fiber on asthma through SCFA production and the resulting decrease in pro-inflammatory cytokines and increase in anti-inflammatory cytokine. This paper will reveal gaps in knowledge in which clinicians may examine how diet can affect inflammatory diseases like asthma.

KEYWORDS: Biomedical and Health Sciences; Nutrition and Natural Products; Asthma; Dietary Fiber; Cytokines.

Introduction

In 2019, 262,000,000 people were affected by asthma and 461,000 of these people died from the condition.[1] Asthma is a disease in which an inflammatory response causes tightening around the airways, leading to symptoms such as chest tightness, wheezing, coughing, and even death due to asphyxiation. This chronic inflammatory disease affects both adults and children.[1,2] The connection between the inflammatory response in asthma and dietary fiber has not been extensively reviewed when taking cytokine pathways and short-chain fatty acids (SCFAs) into consideration. By further examining this process, dietary fiber can be applied as a supplement to asthma treatments and benefit the many people who suffer from asthma.

Dietary fiber, a soluble or insoluble carbohydrate found in plants, has many health benefits including the maintenance of gut health.[3] Dietary fiber, when fermented in the gut, causes the production of many metabolites. Some of these metabolites are SCFAs, which signal immune cells, and most significantly regulate cytokine levels. Because an excess amount of cytokines can have harmful effects as found in many inflammatory diseases, regulating these cytokines can reduce the severity and symptoms of asthma. This study will review the existing research about dietary fiber, SCFAs, and cytokines in the context of asthma to connect dietary fiber to asthma as a potential supplement for asthma treatment.

Discussion

Asthma:

Asthma is a debilitating disease that comes in different forms, therefore, there are many existing therapies to help control asthma symptoms. For long-term asthma, control medications include inhaled corticosteroids and long-acting beta-agonists (LABAs). Inhaled corticosteroids are anti-inflammatory drugs that reduce the swelling of the airways. This therapy can stunt growth in children, as well as cause irritation in the mouth and throat of patients. LABAs, on the other hand, widen the bronchi, and this therapy can only be used as a supplement to inhaled corticosteroids. Therapies that provide fast relief include oral corticosteroids. Oral corticosteroids are used for very severe and sudden symptoms; they have side effects such as stunted growth, osteoporosis (the thinning of bone), cataracts, etc. For allergic asthma, treatments include allergy shots, which initially, are typically administered weekly.[4] There is a need for more treatment options because these therapies do not work for every patient with asthma, some have adverse effects, and some are inconvenient for patients.

The inflammatory response that defines asthma is driven by certain immune cells, the major players being eosinophils, neutrophils, and macrophages. Eosinophils are granulocytes that are signaled to the site of infection, and they are highly active in allergy and asthma. Too many eosinophils in the blood, lungs, and sputum can lead to eosinophilic asthma, in which the respiratory system and airways are blocked. High levels of eosinophils can also lead to a risk of asthma attacks,[5] which include the exacerbation of symptoms due to the tightening of the muscles around the airways.[6] Neutrophils are also granulocytes, and they are highly active in most immune responses. In asthma, neutrophils are initially recruited when the body is experiencing an allergic reaction. Neutrophils cause broncho-constriction and bronchial hyperreactivity, as well as recruit other immune cells that can aggravate the condition. Because they aggravate asthma, clinicians use neutrophils as inflammatory markers.[7] Macrophages are phagocytes, and they can directly engulf and destroy pathogens. However, they are also able to recruit neutrophils and eosinophils, in addition to other immune cells that can worsen the condition.[8]

Other immune cells that drive the inflammatory response in asthma are mast cells and type 2 T helper cells (Th2). Mast cells are recruited by the asthmatic airway smooth muscle and induce bronchial hyper-responsiveness.[9] Th2 cells cause an inflammatory response to harmless particles leading to bronchial hyper-responsiveness.[10] However, one of the driving forces in the inflammatory response of asthma is the role of cytokines, which are chemical messengers for immune cells in asthma.

Cytokines:

Cytokines' effects on inflammation and disease progression are a common topic of discussion in the COVID-19 crisis.[11] Cytokines are peptides that initiate cellular signaling between immune cells and contribute to the immune and inflammatory response. Interleukins (IL), chemokines (CCL), interferon (IFN), and tumor necrosis factor (TNF) are all types of cytokines that function and are secreted differently. Pro-inflammatory cytokines are molecules that signal and recruit immune cells in immune response and inflammation. Though these pro-inflammatory cytokines can help the body fight infection, an excess of these cytokines can harm the body, especially in inflammatory diseases like asthma. Anti-inflammatory cytokines, however, can regulate the secretion and function of pro-inflammatory cytokines and the severity of immune response.[12] Healthy conditions depend on maintaining the proper balance between pro-inflammatory and anti-inflammatory cytokines.

Information about the specific function and role of cytokines in asthma can be found in Table 1. In the lung tissue of patients with asthma, there are increased amounts of cytokines IL-4 and IL-13,[13] and in the sputum, IL-6, IL-8, and IFN-γ are increasingly prevalent.[14] Notably, these cytokines are all proinflammatory. By promoting the growth in eosinophils, neutrophils, mast cells, and histamine, the proinflammatory cytokines trigger the inflammatory response that defines asthma.

Naturally occurring anti-inflammatory cytokines regulate these pro-inflammatory cytokines, but there are also antibody therapeutics that target pro-inflammatory cytokines. Antibody therapeutics allow for the sequestering of pro-inflammatory cytokines, which inhibits these cytokines from reaching their targets and ultimately causing inflammation.

Table 1: The Role, Source and Function of Cytokines in Asthma.

Cytokine	Role in Asthma,[15]	Source,[15]	Function
IL-4	Pro-inflammatory	T cells	Growth in B cells, eosinophils, and mast cells; increase in histamine; histamine-induced Ca2+ mobilization,[13, 15]
IL-5	Pro-inflammatory	Mast cells, Th2 cells	Increased eosinophil production,[15]
IL-6	Pro-inflammatory	Th2 cells and antigen-presenting cells	Increased production of B cells; growth in neutrophils in the sputum; correlation with IL-13 in asthmatics,[15-16]
IL-8	Pro-inflammatory	Macrophages	Attracts T cells and neutrophils,[15]
IL-13	Pro-inflammatory	Th2 cells	Growth in B cells, eosinophils, and mast cells; an increase in histamine; histamine-induced Ca2+ mobilization; increase in neutrophils in the sputum; correlation with IL-6 in people with asthma,[15-16]
IL-33	Pro-inflammatory,[17]	Epithelial cells, macrophages, and dendritic cells,[17]	Activates the Th2 immune response; promotes the growth of eosinophils, macrophages, and pro-inflammatory cytokines,[17]
TNF-α	Pro-inflammatory	Macrophages	Attracts T cells and neutrophils to the site of infection,[15]
INF-γ	Pro-inflammatory	Natural killer and Th1 cells	Activates natural killer cells, macrophages and neutrophils,[15]
CCL5	Pro-inflammatory,[18]	Cytotoxic T cells,[18]	Cytokine production; recruits monocytes, neutrophils, and eosinophils,[18]
CCL17	Pro-inflammatory,[19]	Dendritic cells,[19]	Attracts T cells,[19]
IL-10	Anti-inflammatory	Cytotoxic B and T cells and Th2 cells	Inhibits the production of pro-inflammatory cytokines; increases the production of antibodies; decreases mast cell growth,[15]
IL-35	Anti-inflammatory	Treg, Breg, cytotoxic Treg, and dendritic cells	Inhibits the differentiation of T helper cells; promotes the production of Treg cells,[15]

This table focuses on cytokine activity in asthma specifically. Often, cytokines can have different effects in other disorders that are not described here.[12]

Dupilumab, an anti-4Ra antibody, regulates the function of IL-13 and IL-4, and this has been confirmed to reduce symptoms, delay severe asthma attacks, block the effects of histamine-induced Ca^{2+} mobilization in the bronchi, and increase lung function and forced expiratory volume (FEV%).[20,21] Tralokinumab is a therapy that specifically targets IL-13, and is proven to increase FEV% and lung function.[22] Benralizumab, an antibody for IL-5, reduces the eosinophil count in the airway mucosa, the sputum, bone marrow, and blood of asthma patients.[23,24] These therapeutics help treat asthma by specifically targeting and blocking certain cytokine signaling pathways, but they do not work for every patient with asthma. For example, Tralokinumab, the therapeutic that targets IL-13, cannot be taken along with oral corticosteroids, a treatment that many severe asthma patients take.[22] In addition to being incompatible with some other treatments, there are issues with patient compliance. Tralokinumab, is a home-administered shot; 6 percent of the patients in an initial clinical trial for this therapy discontinued the treatment.[22] These antibody therapeutics also cause various moderate to severe side effects. Dupilumab, the anti-4Ra antibody, causes common symptoms of eye irritation, swelling, burning, and many rare symptoms that can be life-threatening.[21] However, a completely natural, supplementary therapy for asthma, which patients can take without fearing severe risk, is dietary fiber.

Dietary Fiber:

Dietary fiber, which is found in plant foods, has a variety of health benefits. There are two types of fiber, insoluble and soluble, which have different effects. Insoluble fiber is not broken down by water during digestion and it helps maintain regular bowel movements, while soluble fiber, which can be dissolved by water during digestion, is fermentable in the gut and can manage blood sugar, cholesterol, gut health, and more.[25] Fiber is accessible, and there are many sources of fiber including grains, fruits, and vegetables.[3] A fiber-rich diet can increase stool bulk, regulate blood pressure,[26] reduce symptoms of depression,[27] and prevent different types of cancer.[28,29] Regular dietary fiber consumption also leads to a to a more balanced gut micro-biome which, in turn, improves the body's overall health.[3]

One of the byproducts of the fermentation of soluble dietary fiber in the gut are SCFAs, the most abundant being butyrate, acetate, and propionate. SCFAs affect immune response through signaling to immune cells. For example, dietary fiber is known to up-regulate the messenger RNA (mRNA) of G-protein coupled receptors (GPCRs), such as GPCR41 and GPCR43, which are SCFA receptors.[30] The activation of these SCFA receptors in neutrophils and macrophages by dietary fiber leads to lower inflammation.[31] Notably, SCFAs lead to a modulation of cytokines, and this process potentially reduces the severity of the inflammatory response in asthma.[32]

Dietary Fiber as a Potential Asthma Therapy:

As clinicians have found dietary fiber to benefit inflammatory conditions such as inflammatory bowel disease,[33] and depression,[27] they have started to investigate the connection between dietary fiber and asthma, another chronic inflammatory disease. In a clinical study, which explores the effects of the soluble fiber inulin on asthmatic adults, dietary inulin supplements over the span of 7 days result in a significant improvement in asthma control. This is shown by decreasing levels of airway eosinophils in the sputum in addition to increasing amounts of plasma SCFAs.[34] Within four hours of the consumption of 3.5 grams of inulin, inflammatory markers such as neutrophils, eosinophils, and macrophages significantly decrease in the sputum, while GPCR41 and GPCR43 increase in the sputum.[30] A dust mite-induced asthma model in mice had similar results in which the same inflammatory markers were significantly reduced due to soluble galacto-oligosaccharides (GOS).[35] Insoluble oligosaccharides such as acidicoligosaccharides (AOS) and fructo-oligosaccharides (FOS) mixed with bifidobacterium, a probiotic, reduce airway inflammation, eosinophils, and inflammatory cells in chronic asthma.[36] Multiple clinical studies note better lung function through increased FEV% in people with high fiber intake.[30,37] These studies utilize different types of fiber, such as inulin, GOS, AOS, and FOS, to not only examine the connection between dietary fiber and inflammatory markers, but also the connection between dietary fiber and increased lung function. Therefore, it is evident that fiber improves the condition of asthma.

Cellular signaling by cytokines initiates the inflammatory response that defines asthma. The clinical study by Zhang and Bai evaluated levels of the pro-inflammatory cytokine IL-8 in asthmatic and non-asthmatic patients and found that IL-8 is significantly higher in patients with asthma,[38] and another clinical study showed that inulin decreases the amount of IL-8 in the sputum.[30] Similarly, a mouse model showed that GOS leads to the decrease of the pro-inflammatory cytokines CCL5, CCL17, IL-33, IL-13, and IL-6 in the lung tissue of asthma patients.[35] Additionally, the same pattern occurred in another mouse model with the pro-inflammatory cytokines IFN-γ, IL-5, IL-13, and IL-4.[39] These studies show that fiber intake leads to a decrease in these pro-inflammatory cytokines that help fuel the inflammatory response of asthma. The question remains, how do inulin, GOS, and other dietary fibers lead to a decrease in pro-inflammatory cytokines?

One potential mechanism is through SCFAs, which affect cytokine production by both inhibiting proinflammatory cytokines and increasing the production of anti-inflammatory cytokines. SCFAs are a product of the fermentation of dietary fiber, and it is clinically shown that people with low-fiber diets have a higher white blood cell count and IL-6 levels.[40] Another clinical trial measured SCFA and cytokine levels in the elderly and found that increased butyrate production causes decreasing TNF-α levels.[41] Scientists must consider butyrate, which is gaining recent attention by the scientific community, because by decreasing pro-inflammatory cytokine levels it may help treat asthma.

SCFAs also increase the production of anti-inflammatory cytokines. In an *in vivo* study, 200 mM of the SCFAs acetate and propionate were added to the drinking water of mice three times a week. This method led to an increase in regulatory T cells,[39] which secrete anti-inflammatory cytokines such as IL-35 and IL-10.[43] As acetate and propionate lead to an increase in certain anti-inflammatory cytokines, they are a great therapeutic target for an inflammatory disease like asthma. Similar to previously discussed inflammatory disorders, cereal dietary fiber consumed by obese and overweight people can decrease IL-6 and TNF-α, and increase levels of IL-10, an anti-inflammatory cytokine.[43] By both decreasing pro-inflammatory cytokine levels and increasing anti-inflammatory cytokine levels, SCFAs inhibit the inflammation in asthma (Figure 1).

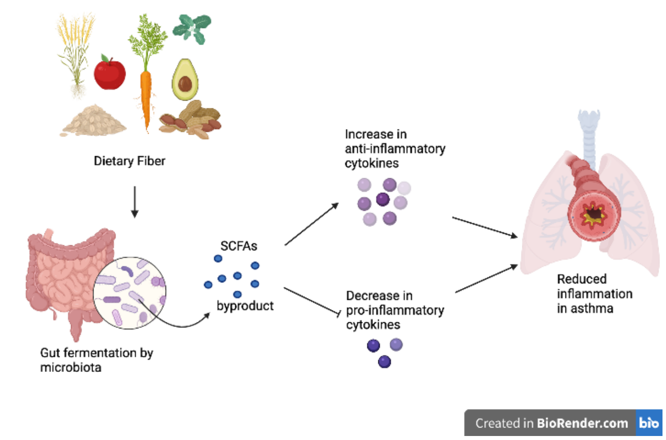

Figure 1: Dietary Fiber Reduces Inflammation in Asthma.

Based on the evidence presented, SCFAs likely decrease levels of the cytokine IL-6 as *in vivo* and clinical data agree.[35,40] However, when examining the cytokine TNF-α, the data are not as clear. An *in vitro* study by Rutting *et al.* shows a decrease in TNF-α when butyrate, propionate, and acetate are present,[44] but in clinical studies, the opposite is seen.[41] The cause of these different behaviors of SCFAs and their relationship with cytokines is evident, yet not explained, making this a gap that should be further examined.

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Conclusion

Evidence is mounting for the possibility of dietary fiber as a good lifestyle change for patients with asthma through its production of SCFAs, and the resulting regulation of cytokines that leads to anti-inflammatory effects. The *in vitro*, *in vivo*, and clinical data reviewed in this paper support the idea that dietary fiber can benefit patients with inflammatory diseases such as asthma. Recent data indicate that dietary fiber can reduce the number of inflammatory cells, such as eosinophils and neutrophils in the lung airways and sputum.[30, 34-36] Current data also indicate increased lung function (shown by increased FEV%) in cases of asthma treated with dietary fiber.[30, 37]

One mechanism of fiber's effect on inflammation may be through the production of SCFAs as a result of the fermentation of soluble fiber found in legumes, grains, fruits, and vegetables. This is supported by research findings that show increased amounts of plasma SCFAs as well as SCFA receptors in cases of asthma treated with dietary fiber.[30, 34] SCFAs specifically improve asthma in patients through cytokine regulation; studies show that SCFAs decrease pro-inflammatory cytokines and increase anti-inflammatory cytokines. Research supports that proinflammatory cytokines are more prevalent in cases of asthma, but they decrease when the asthma is treated with SCFAs as shown with IL-8.[30, 38] Inversely, anti-inflammatory cytokines are not as prevalent in cases of asthma, yet they increase when an asthma patient is treated with SCFAs, as shown with IL-35 and IL-10.[38, 42]

Current therapies are not sufficient to control asthma in all patients, so clinicians are searching for supplementary therapies. The novel cytokine-targeting antibody therapies proved successful in bettering conditions of asthma in patients, but also carried unintended negative impacts from harmful side effects.[22, 26] Because of the prevalence of these negative side effects, it is crucial to continue to search for effective, low-risk therapies. Thus, the investigation into the significance of dietary fiber and diet as possible supplementary therapies for inflammatory diseases like asthma must continue. These therapies would enhance the success of pre-existing asthma therapies, all while being both low risk and accessible for everyone.

Although basic, mechanistic research linking dietary fiber with asthma exists in animal models, clinical research is limited. Hence, more clinical research is needed to confirm the efficacy of dietary fiber. Additionally, existing clinical research does not investigate long-term implications of dietary fiber in their asthmatic participants. The effect of dietary fiber on asthma in the pediatric population should also be researched, especially considering that about 6 million children currently suffer from asthma. Lastly, many studies consider various types of dietary fiber in the context of inflammation, so the beneficial effects of specific forms of dietary fiber should be studied and compared.

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