*Supplement Article*

# Emerging science on whole grain intake and inflammation

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*Although the biological mechanisms surrounding the widely reported association between whole grain (WG) consumption and reduced risk of several diseases are not fully understood, there is growing evidence suggesting that inflammation may be an essential mediator in this multifaceted process. It also appears that several mechanisms influence the modulatory actions of WGs on inflammation, including the effect of fiber, phytochemicals, and their microbial-derived metabolites. While some of these effects are direct, others involve gut microbiota, which transform important bioactive substances into more useful metabolites that moderate inflammatory signaling pathways. This review evaluates emerging evidence of the relationship between WGs and their effects on markers of subclinical inflammation, and highlights the role of fiber, unique WG phytochemicals, and gut microbiota on the anti-inflammatory effects of WG intake.*

## INTRODUCTION

Epidemiological studies strongly support the evidence that whole grain (WG) consumption is associated with a reduced risk of chronic diseases such as coronary heart disease, cardiovascular diseases, type 2 diabetes, and total cancer, and mortality due to any cause.[1–4] Although the mechanisms for this beneficial effect are not fully understood, the role of subclinical inflammation as a common denominator in most disease processes is gradually gaining attention in the literature.[5,6] This recognition has been accompanied by efforts to examine the action of whole grains on the inflammatory process as a possible explanation for the ability of whole grains to moderate the risk and severity of several diseases.[7,8]

Inflammation may be defined as a complex series of physiological responses to infections, noxious stimuli, injuries, and toxins, which usually lasts for a few hours or days.[9–13] In its chronic form, this response lingers over an extended period, with negative impacts on tissues and organs.[14,15] Genetic susceptibility, psychological stress, and lifestyle choices, along with poor dietary patterns, contribute to chronic inflammation.[16–18] Nonsteroidal anti-inflammatory drugs are commonly used to treat a number of inflammatory states and diseases. However, these groups of drugs have come under scrutiny because of the recent focus on the adverse effects accompanying their consumption, including damage to the duodenum, increased risk of cardiovascular events, and acute kidney injury.[19–23] Moreover, these drugs reduce the pain and symptoms of inflammation and often fail to eliminate causal pathogenic agents.[24] The presence of these pathogens may cause low-grade chronic inflammation, a key risk factor in a host of health problems and several major diseases.

Nevertheless, there is an exciting prospect that bioactive compounds from WGs (Figure 1), with fewer side effects, may help attenuate inflammation and reduce the risk of many inflammation-associated diseases. Although there may never be such a single path to the prevention of inflammation-induced diseases, it is possible that the long-term ingestion of WG products as part of an overall healthy dietary pattern may contribute

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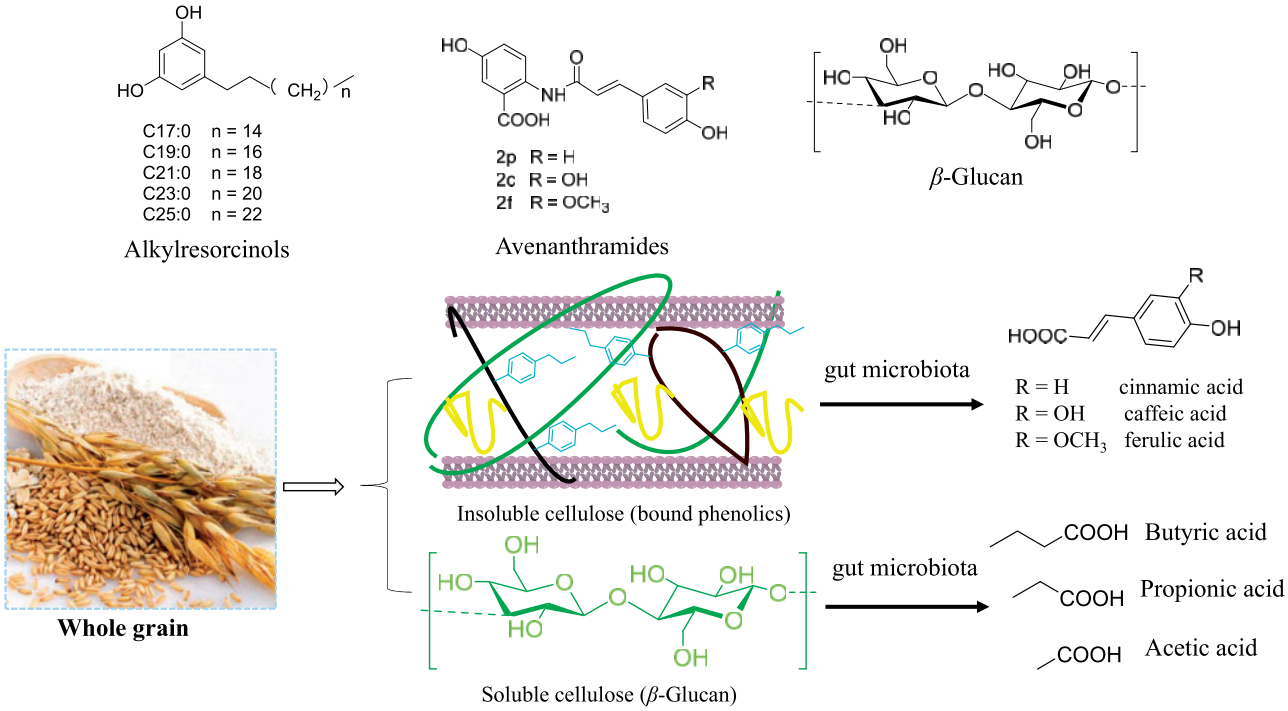


*Figure 1* **Structures of the components in whole grains (alkylresorcinols, avenanthramides, and β-glucan) and the microbial metabolites of fiber: free phenolic acids and short-chain fatty acids**

to a significant reduction in the development of chronic inflammation–related diseases. This review summarizes the current knowledge of the association between WG intake and biomarkers of inflammation and presents a perspective on this interaction.

## EFFECTS OF WHOLE GRAIN INTAKE ON INFLAMMATION: EVIDENCE FROM RODENT STUDIES

There are very limited rodent models available for the purpose of evaluating the ability of WGs to moderate different inflammation risk factors. Murtaza et al[25] examined the effect on inflammation biomarkers of adding finger millet whole grain (FM-WG) and finger millet bran (FM-BR) to the feeding regimen of high-fat diet (HFD)-fed LACA mice for 12 weeks. The FM-WG and FM-BR dietary intervention reduced interleukin (IL)-1β concentrations and adipose inflammation in the HFD-fed mice. While the FM-BR–supplemented diet decreased the expressions of genes involved in inflammation, like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), macrophage inflammatory protein-1 alpha, tumor necrosis factor (TNF)-alpha (TNF-α), monocyte chemoattractant protein-1, ADAM8 (a disintegrin and metalloproteinase domain 8), epidermal growth factor–like module-containing mucin-like hormone receptor (EMR)1 (F4/80), cluster of differentiation 68, inducible nitric oxide synthase, and IL-6, the FM-WG–supplemented diet reduced the expressions of NF-κB, macrophage inflammatory protein-1 alpha, TNF-α, F4/80, CD68, and inducible nitric oxide synthase, but slightly increased the expressions of IL-6 and ADAM8, in white adipose tissue. IL-6 has been shown to have dual functions – both pro-inflammatory and anti-inflammatory – depending on the particular cell and inflammation condition, which could in part explain the observed results.[26] In a similar study, diets containing 2 WG barley varieties, SW and Hadm, differing in dietary fiber and β-glucans content and also in the solubility of dietary fiber, were fed to male Wistar rats, following which their anti-inflammatory properties were tested.[27] Intake of barley reduced inflammation, as evidenced by observed lower levels of plasma LPS-binding protein and monocyte chemoattractant protein-1.

## EFFECTS OF WHOLE GRAIN INTAKE ON INFLAMMATION: EVIDENCE FROM HUMAN STUDIES

As inflammation becomes increasingly recognized in the pathophysiology of most diseases, epidemiological and human intervention studies have been used to explore the modulatory effects of WG diets on biomarkers of inflammation. The realization that elevated levels of the inflammation biomarkers C-reactive protein (CRP), TNF-α, TNF-α receptor-1 and receptor-2, IL-6, fibrinogen, and IL-1β are associated with type 2 diabetes, cardiovascular disease, and cancer have made these

biomarkers a target of most observation and intervention studies. In most studies exploring the effect of WGs on inflammation, IL-6 appears to be the most examined inflammation biomarker, followed by CRP, an acute-phase protein secreted by the liver in response to IL-6.[28,29]

The impact of increased WG consumption on the biomarkers of inflammation, in randomized controlled trials (RCTs) involving healthy participants, produced mixed results. In a 3-week study involving 15 healthy participants (12 men and 3 women) who were randomly assigned into 2 isoenergetic diets rich in whole wheat and refined wheat products (cereal fiber 23.1 vs 9.8 g/d), there was no observed alteration in high-sensitivity C-reactive protein (hs-CRP), a biomarker of inflammation, between whole wheat and refined wheat consumptions.[30] A similar overnight crossover study among 21 healthy subjects also failed to show any association between an increased WG diet and IL-6 levels.[31] Andersson et al[21] also compared the effects of WG diets with diets containing the same amount of refined grains on several markers of inflammation. This 6-week WG consumption among healthy moderately overweight adults (22 women and 8 men) in the randomized crossover study did not affect IL-6 and CRP levels in plasma, and neither did substitution of WG (mainly based on milled wheat) for refined-grain products affect inflammation biomarkers.[21] In contrast, a cohort study involving 259 healthy women aged 18–44 years revealed an inverse association between WG intake and hs-CRP concentrations. In the design of this particular study, a serving consisted of 16 g of a 100% WG food. Results showed that participants who consumed 0–1 serving of WG per day had, on average, 11.5% lower hs-CRP concentrations, while participants who consumed $\geq 1$ serving per day had 12.3% lower hs-CRP concentrations than non-consumers. Also, women who consumed $\geq 1$ serving per day of WG had a lower probability of having moderate or elevated hs-CRP concentrations than nonconsumers.[32] In another RCT (49 men and 32 postmenopausal women), Vanegas et al[33] found that 6-week WG consumption had a modest effect on gut microbiota and short-chain fatty acid (SCFA) compositions, as well as on certain indicators of the immune response in healthy middle-aged adults, but no effect on plasma/stool inflammatory cytokine or plasma lipopolysaccharide-binding concentrations. In another WG and refined grain consumption study in human subjects free of type 2 diabetes (n = 941) using cross-sectional data from the Insulin Resistance Atherosclerosis Study, Masters et al[34] found that WG intake was inversely related to log plasma plasminogen activator inhibitor type-1 (PAI-1; $\beta = -0.102$; standard error of the mean = 0.038; $P = 0.0077$) and log CRP ($\beta = -0.102$; standard error of the mean = 0.048; $P = 0.0340$), but these relationships were attenuated by the addition of metabolic risk factors such as insulin sensitivity, waist circumference, and 2-hour post-load glucose to the model. Refined grain intake showed a positive association – independent of demographic, lifestyle, and dietary variables – with plasma PAI-1 concentrations, while no association was observed for fibrinogen with either WG or refined grain intake.

In most observation and intervention studies among unhealthy participants, the effect of WG diet on inflammation biomarkers is more evident. In a study involving 902 diabetic women, WG or bran consumption was associated with a significantly decreased trend in some inflammation biomarkers.[35] Results from this study indicated a reduction in the concentrations of CRP and TNF receptor-2 by 18% and 8%, respectively, among adults in the highest quintile of WG intake as compared to the lowest quintile. However, no significant association was found between WG intake and reductions in the levels of adhesion molecules, E-selectin, and ICAM-1 (intercellular adhesion molecule-1), considered as nondirect inflammatory markers in some studies.[36,37] In contrast, Wolever et al[38] observed decreased serum levels of CRP (−21.8% vs +12.1%), and of the adhesion molecules ICAM-1(−28.4% vs +6.3%), serum amyloid A (−17.4% vs +9.9%), and leptin (−9.7% vs +39.2%), after an increased consumption of WG diet. Furthermore, there are reports showing a reduction in the levels of CRP upon consumption of WG diets when compared with refined-grain diets in patients with type 2 diabetes.

Xu et al[39] conducted a meta-analysis on data from several randomized controlled trials to examine the association between WG consumption and circulating inflammatory markers. A total of 9 RCTs, with data on 838 participants, were included in the meta-analysis. Results from these analyses revealed that increased consumption of WGs was inversely associated with changes in the inflammatory markers CRP, IL-6, TNF-α, and IL-1β (standardized mean difference, 0.16; 95% confidence interval [CI], 0.02–0.30). Specific analyses also yielded an inverse association between WG consumption and significant decrease in the concentrations of CRP (standardized mean difference, 0.29; 95%CI, 0.08–0.50) and IL-6 (standardized mean difference, 0.19; 95%CI, 0.03–0.36). Likewise, in a similar meta-analysis, involving 13 studies with 466 participants, WG consumption was also found to have a significant effect on serum concentrations of hs-CRP and IL-6, but no significant effect on TNF-α.[40]

In another intervention study, Zamaratskaia et al[41] evaluated the effects of WG diet on low-grade inflammation biomarkers in men with prostate cancer.

Seventeen men with untreated, low-grade prostate cancer were given 485 g/d of WG rye and rye bran products or refined wheat products with added cellulose. Results from this study showed that consumption of WG rye and rye bran lowered the inflammation biomarkers TNF receptor-2, E-selectin, and endostatin, compared with consumption of diets comprising refined wheat product in men with prostate cancer. A positive effect of WG consumption on subclinical inflammation was observed when 50 obese participants (body mass index $> 30\,kg/m^2$) consumed WG-rich diets for a period of 12 weeks. At the completion of the intervention, CRP concentrations had declined considerably, by 38%, in the WG group, but were unaffected in the refined-grain group.[42] Kopf et al[43] compared the effect of WG or fruit and vegetable diets on 49 subjects with overweight- or obesity-related issues. Results from this study indicated that a 3 servings per day WG consumption for 6 weeks resulted in a significant decrease in TNF-α (−3.7 pg/mL, $P < 0.001$) and lipopolysaccharide-binding protein (−0.2 μh/mL, $P = 0.02$), whereas no significant changes from baseline values were found for hs-CRP and IL-6. Another RCT conducted over two 8-week WG ($179 \pm 50$ g/d) dietary intervention periods, in a subset of 50 adult participants at risk of developing metabolic syndrome, also demonstrated decreases in body weight ($P < 0.0001$) and fasting serum concentrations of the pro-inflammatory cytokines IL-6 ($P = 0.009$), CRP ($P = 0.003$), and IL-1β ($P = 0.008$), although TNF-α remained unchanged, compared with the refined-grain diet. Moreover, the reduction in IL-6 was found to be associated with the amount of WG consumed, in particular with intake of rye.[44]

## EFFECTS OF WHOLE GRAIN INTAKE ON INFLAMMATION-ACTIVE COMPONENTS

### Fiber: microbial-derived metabolites (short-chain fatty acids)

WGs are good sources of soluble dietary fiber, especially β-glucan, which has outstanding functional and nutritional properties. β-glucan is considered to be a major active component of WGs, leading to changes in, and stimulation of, gut microbiota (Figure 2). Increased consumption of dietary fiber has been reported to proffer several beneficial effects, including anti-inflammatory effects. There are also reports of a direct association between carbohydrate-rich and dietary fiber–deficient diets in the promotion of inflammation, thus giving credence to fiber's important impact on inflammation.[45,46] Qi et al[35] evaluated the effect of WG fiber on markers of inflammation and found an inverse association between the highest and lowest quintile of cereal fiber intake with lower levels of CRP and TNF receptor-2 concentrations (18% and 8%, respectively). The effect of β-glucan from WG product has also been investigated in ulcerative colitis. Ulcerative colitis is a major inflammatory bowel disease characterized by inflammation within the gastrointestinal tract and caused by a chronic or relapsing immune system activation. Upregulation of certain pro-inflammation marker, such as IL-1β, has been reported in both colitis patients[47] and also in animal models.[48] The pro-inflammation biomarker IL-1β is a focus of most studies on colitis since it is one of the primary drivers of inflammation and is mainly produced by lamina propria monocytes, including macrophages, infiltrating the colitis mucosa.[49] Liu et al[50] examined the protective effect of oat β-glucan against colitis induced by dextran sodium sulfate in 80 mice. The outcome of this study revealed a decrease in aberrant mRNA expression of the inflammation biomarkers TNF-α, IL-6, and IL-1β after an oat β-glucan (500 mg/kg and 1000 mg/kg β-glucan) intervention diet. In a related study, Wilczak et al[51] investigated the influence of 2 forms of β-glucan (high molecular weight oat β-glucan and low molecular weight oat β-glucan) on 72 male Sprague–Dawley rats with LPS-induced enteritis. Results from this study, as evidenced by pro-inflammatory (IL-12, TNF-α) data, anti-inflammatory markers, and the profiles of both populations of lymphocytes (intraepithelial and lamina propria) residing in the colon tissue, indicated a strong anti-inflammatory property of β-glucan, especially the low molecular weight oat β-glucan.

The products of microbial degradation of WG dietary fiber, SCFAs, have also been credited for the ability of WGs to modulate inflammation (Figures 1 and 2). The bioactive effects of SCFAs may partly explain the therapeutic effect of WGs against inflammation. It has been reported that WG consumption increases the concentration of *Lachnospira* (an SCFA producer) and stool SCFA concentration, compared with refined-grain consumption, further expounding on the importance of SCFAs in moderating inflammation.[52] SCFAs (butyrate, propionate, and acetate) in the gastrointestinal tract and blood can prevent inflammation by regulating the functions of leukocytes and production of cytokines. Cytokines are intercellular messengers and a source of soluble regulatory signals that initiate and constrain inflammatory responses via signaling pathways – in particular, NF-κB and mitogen-activated protein kinase. Cytokines migrate to the foci of inflammation to destroy the microbial pathogens.[53] However, while cytokines play an essential role in coordinating the development of innate and adaptive immune responses to inflammation, when in excess they may become life-threatening. Incidentally, SCFAs can also impact the

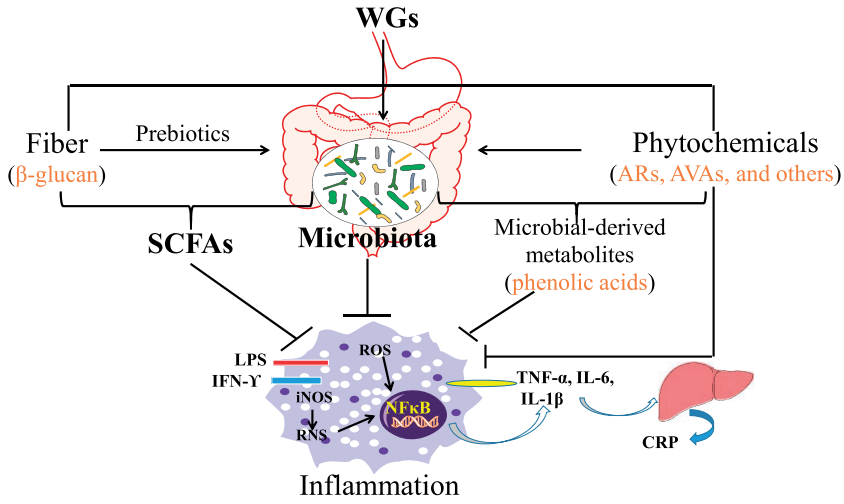


*Figure 2* **Overview of the anti-inflammatory properties of WGs in different pathways.** *Abbreviations:* ARs, alkylresorcinols; AVAs, avenanthramides; CRP, C-reactive protein; IFN-ϒ, interferon gamma; IL-1*β*, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; TNF-α, tumor necrosis factor alpha; WGs, whole grains

functions of histone deacetylase. Histone deacetylase inhibitors have been reported to reduce cytokine levels in plasma and also decrease ex vivo responses to pro-inflammatory stimuli.[54,55] Recently, several reports have been published describing the ability of SCFAs to activate immune cells, which helps destroy inflammation-triggering pathogens on the one hand, while on the other also controls the production of cytokines and chemokines when in excess.

## Phytochemicals: alkylresorcinols, avenanthramides, and microbial-derived metabolites (phenolic acids)

In a bid to understand the impact of WGs on inflammation, several bioactive components of WGs and their metabolites have been examined for likely impact on inflammation indicators.[56–59] Although previous studies have mainly credited the presence of fiber in WGs for their anti-inflammation effect, current research suggests that anti-inflammatory agents in WGs go beyond fiber.[60–63] Notably, other bioactive compounds in WGs, including phenolic compounds, tocols, folates, and phytosterols, have also been implicated in the anti-inflammatory impact of WGs.

Reactive oxygen species, including superoxide, hydrogen peroxide, and hydroxyl radical, promote the synthesis of pro-inflammatory cytokines, which in turn promotes inflammation. Remarkably, phytochemicals in WGs and their metabolites have been reported to moderate inflammation by altering the actions of reactive oxygen species. Possible mechanisms for this effect may include the ability of WG phytochemicals, especially phenolic compounds, to act as antioxidants, interfere with oxidative stress signaling, and suppress pro-inflammatory signaling transductions. Phytochemicals in WG do not only directly react with reactive oxygen species, but may also agonistically activate cellular signaling pathways.[64,65] Some unique phytochemicals in WGs, including alkylresorcinols (ARs) in WG wheat and rye and avenanthramides (AVAs) in WG oat (Figure 1), have been the subject of most research owing to their health-promoting benefits, including their impact on biomarkers of inflammation.

Epidemiological studies have been conducted on ARs, a major phenolic compound in WG wheat and rye comprising a resorcinol-type phenolic ring and a long odd-numbered aliphatic chain made up of 17–25 carbon atoms (Figure 1). ARs have also been identified as the exposure biomarkers for WG wheat and rye intake in epidemiological studies.[66] The anti-inflammatory effects of ARs have been reported in several in vitro and in vivo studies (Figure 2). Liu et al investigated the anti-inflammatory activity of ARs from 21 wheat bran samples with AR content ranging between 697 μg/g and 1732 μg/g dry bran. The analyzed samples were composed of 5 different homologues, among which C19:0 and C21:0 were the most abundant, followed by C17:0, C23:0, and C25:0.[67] Results from this study showed a notable decrease in NF-κB p65 nuclear translocation and inhibitor κB kinase and Jun N-terminal kinase phosphorylation after the treatment of ARs to LPS-treated macrophage RAW 264.7 cells, which is a very popular in vitro model of inflammation. However, no significant correlation was found between the AR homologue content and anti-inflammatory activity except for index TNF-α, where the strongest correlative

value was obtained between TNF-α and C17:0. Findings from this study suggested that perhaps only C17:0 AR analogue contributes to a TNF-α–mediated inhibitory effect on inflammation, a likely explanation being that the AR homologue C17:0 has a higher solubility than other long-chain homologues.[68] Similar findings were reported by Roager et al,[44] who found a negative association between serum IL-6 and plasma concentrations of the AR homologues C17:0 and C19:0, the main homologues in rye products. In addition, IL-6 was also negatively associated with the ratio of plasma AR homologues C17:0-to-C21:0, suggesting that the reduction in IL-6 was mainly associated with rye intake.

AVAs, a unique type of compound present in oat and located in the bran fraction of oat grain, have also been examined for their health-promoting properties, including their anti-inflammation property. The 3 most abundant AVAs in oat are esters of 5-hydroxyanthranilic acid with *p*-coumaric acid (2p or AVA-A), ferulic acid (2f or AVA-B), or caffeic acid (2c or AVA-C) (Figure 1). AVAs, the phenolic compound in oat, have also been reported to exhibit both antioxidant and anti-inflammatory effects. The antioxidant and anti-inflammatory activities of AVAs have been reported in both in vitro and in vivo studies (Figure 2). AVA supplementation was found to significantly decrease the systemic pro-inflammatory response in exercise-induced inflammation in both younger and older women.[69] In this study, there was an observed decrease in neutrophil respiratory burst, CRP, IL-1β, IL-6 levels, and NFκB activation following AVA treatment. Liu et al[70] also investigated the anti-inflammatory and antiatherogenic effects of oat AVAs in the human aortic endothelial cell culture system. Pretreatment of human aortic endothelial cells with a mixture of AVAs for 24 hours significantly suppressed IL-1β-stimulated inflammation. Additionally, Sur et al[71] explored the possible anti-inflammatory effects of AVA in human keratinocytes. Results from this study revealed a significant inhibition of NF-κB-dependent luciferase activity following AVA treatment and a subsequent reduction in the release of IL-8 in TNF-α-treated keratinocytes.

Phenolic acids and their circulating metabolites have also been reported to possess anti-inflammatory effects ex vivo. Mateo Anson et al[72] conducted a study that evaluated the effect of phenolic acids and their metabolites on the biomarkers of inflammation. In this study, 8 healthy men consumed a low-phenolic-acid diet for 3 days, and upon an overnight fasting, consumed either 300 g of whole wheat bioprocessed bread containing high concentration of phenolic acids or normal wheat bread with low phenolic acid concentrations. Following 0 (baseline), 1.25, 6, and 12 hours' bread ingestion, blood samples were drawn and incubated with LPS. Examination of different blood samples showed a significantly lower pro-inflammatory to anti-inflammatory cytokine ratio in LPS-stimulated blood – obtained after the consumption of bioprocessed wheat bread with high-phenolic-acid content – than the bread with low-phenolic-acid content.

## EFFECTS OF WHOLE GRAIN INTAKE ON INFLAMMATION: ROLE OF GUT MICROBIOTA

The ability of WGs to affect both host metabolism and gut microbial ecology suggests that some benefits of WGs are mediated through the effects of WGs on the gut microbiome (Figure 2). Some nutritional studies have therefore assessed the effect of WGs on inflammation, and the role of the gut microbiome in this intervention. Findings from a study by Lee et al[73] revealed a modulatory effect of WGs on inflammation markers and also showed changes in the population of useful microbiota such as *Lactobacillus* and *Bifidobacterium*, together with a lower abundance of the *Bacteroides fragilis* group of bacteria in the cecum. Additionally, Vitaglione et al[74] reported that significant reduction in the inflammatory marker TNF-α was associated with increase in the abundance of *Lactobacillus* and *Bacteroides* spp. Moreover, Martínez et al[75] also examined whether the effect of WGs on inflammation biomarkers was associated with the gut microbiome. This study was conducted to include a 4-week treatment in which 28 healthy adults consumed a daily dose of 60 g of WG barley, brown rice, or an equal mixture of the two. Results from this study showed a reduction in plasma IL-6 levels, and a tendency for a decrease in plasma hs-CRP levels. These reductions were characterized by increases in the genera *Roseburia, Bifidobacterium*, and *Dialister*, and the species *Eubacterium rectale* and *Roseburia faecis*. Supplementation with FM-WG and FM-BR in HFD reversed the microbial derangements induced by HFD in mice and exerted a "prebiotic effect," similar to increasing the abundance of *Lactobacillus*, *Bifidobacterium*, *Akkermansia,* and *Bacteroides-Prevotella* spp. Moreover, HFD-bran and HFD-WG feeding increased the abundance of *Roseburia spp*., important butyrate-producing bacteria in the gut, which may have stimulated butyrate-dependent anti-inflammatory effects, and also decreased abundance of Enterobacteriaceae, which may be associated with a decrease in LPS translocation and an improvement in gut barrier function. Similarly, AR supplementation significantly increased the amount of *Prevotella* spp. and reduced the amount of *Enterococcus* spp.; such prebiotic effects may have been involved in the anti-inflammatory effects and metabolic improvements observed in the HFD-fed mice.[76]

## CONCLUSION

In conclusion, studies on the effect of WGs on inflammation have been inconclusive, likely because of the differences in study approaches and designs. For example, while some studies completely controlled the diet, maintained weight, and kept dietary components to be examined constant, other studies were not so controlled. Furthermore, some study designs did not include biomarkers of adherence, which may influence the observed impact of WGs on inflammatory markers. Also, while some studies were conducted among healthy individuals who were not likely to be immune compromised or to have high inflammatory status, it is possible that more-pronounced changes would have been observed in participants preselected for having high inflammatory status or chronic disease.

Also, it appears that several mechanisms influence the modulatory actions of WGs on inflammation. These actions may include the effects of fiber, microbial metabolites SCFAs (associated with fiber), phytochemicals, and their metabolites. While some of these effects are direct, others involve the prebiotic effects on gut microbiota that transform important bioactive substances to more useful metabolites, which, in turn, affect inflammatory biomarkers.

In general, WGs contain both fiber and phytochemicals. These actions of WGs on inflammation include not only the beneficial effects of fiber, but also the direct anti-inflammatory and antioxidant effects of phytochemicals in WGs. Moreover, gut microbiota also play an important role in the anti-inflammatory effects of WGs. The interaction between WGs and microbiota should be considered when interpreting the data and making conclusions in future studies.


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