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EDITORIAL

Can Psyllium Alleviate Colitis?

When thinking of a healthy, well-balanced diet, most people would agree that "eating your greens" is perhaps the best approach one could follow. Dietary fibers indeed are well recognized for their ability to promote health, and recent studies have shown that a high intake of fibers significantly reduces mortality related to a number of diseases with a high incidence in Western population, including heart attack, coronary heart disease and other cardiovascular pathologies, colorectal and breast cancers, and type 2 diabetes, among others.[1,2] However, not only are the mechanisms behind these effects still not fully understood, but *dietary fibers* also is a broad term, englobing a variety of complex carbohydrates, mostly derived from plants, with distinct structural and biochemical properties. Dietary fibers can be divided into 2 major groups: insoluble fibers, whose effects rely mostly on adding bulk to the fecal mass, improving intestinal motility, and binding of noxious substances; and soluble fibers, carbohydrates that provide important bacterial metabolites after gut microbiota fermentation, thus impacting host responses both locally and systemically.[3] Cellulose, hemicellulose, and lignin are examples of insoluble fibers, while guar gum, psyllium, inulin, pectin, and fructooligosaccharides are examples of soluble fibers. Studies on dietary fibers show large variability[4] and sometimes even are contradictory, making it difficult to establish safe and accurate guidelines for fiber consumption because their effects seem to be strongly context-dependent. This might be explained by several reasons, including the different types of targeted fibers, their concentration, the duration of the dietary interventions, the direct and/or indirect correlations of the fibers with other variable elements present in the diet composition, as well as the wide variation in the gut microbial composition among animals raised in different facilities and people of different age, location, and lifestyle.[5]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Bretin et al[6] aimed to identify specific soluble fibers that can protect mice against experimental models of colitis without showing detrimental effects to the host. To this end, they compared the responses of animals fed with different panels of fiber-enriched diets with colitis induced by dextran sulfate sodium (DSS) or T-cell transfer. They observed that although the presence of inulin, cellulose, pectin, and glucomannan exacerbated the severity of DSS colitis to some extent, both psyllium and Hi-maize were able to alleviate the symptoms, yet psyllium showed the strongest protection, ameliorating colitis-related inflammation even at concentrations as low as 2%. The intake of psyllium also significantly impacted the gut microbiota by reducing the total bacterial load and the α-diversity of the bacterial community, with the loss of several members of Firmicutes and Proteobacteria and increased levels of Clostridiaceae, a unique phenotype that is contrary to those observed in animals fed with inulin. Surprisingly, the protective responses of psyllium were not mediated by interleukin 22, a cytokine largely regulated by the gut microbiome,[7] and were not dependent on microbial fiber fermentation.

Next, Bretin et al[6] sought to identify the host pathways involved in the protection driven by psyllium. By performing transcriptomic profiling of colonic cells, they observed that psyllium altered the gene expression of several functional categories, including genes related to bile acid secretion. Psyllium has long been recognized by its ability to bind to bile acids and prevent its reabsorption[8]; however, bile acid sequestration approaches failed to recapitulate the suppression of DSS colitis achieved by psyllium. Notwithstanding, psyllium-fed mice had increased levels of total bile acids in the serum, which was shown to further activate the bile acid sensor Farnesoid X receptor (FXR), a receptor that already has been reported to be involved in the alleviation of colitis severity, although the specific cell type involved in this process still is unclear.[9,10] The investigators validated this correlation in their murine model by showing that the use of the FXR agonist obeticholic acid ameliorated DSS-induced inflammation, while the opposite effect was achieved by using the FXR antagonist glycol-β-muricholic acid. Moreover, psyllium-induced protection to colitis was abolished in FXR-deficient mice, but conditional depletion showed that FXR expression in epithelial cells and hepatocytes does not contribute to this phenotype. According to the investigators, they currently are generating distinct tissue-specific FXR-deficient mice, aiming to identify the cell types in which FXR activation is crucial to lead to colitis protection. Altogether, these results highlight the role played by psyllium, a semisoluble, Plantago seed–derived fiber, in restoring gut health, showing that its intake modifies the gut microbiome, enhances the levels of bile acids in the serum, and activates FXR signaling, thus preventing the harmful effects of colitis without triggering other potential fiber-related deleterious phenotypes.

An interesting parallel can be made with a recent study published by Artis et al[11] showing that a high intake of inulin also strongly up-regulated the levels of bile acids in the serum of mice, an effect that was associated with increased type 2 inflammation both in the gut and lungs, and required FXR activation and the bacterial enzyme bile salt hydrolases. In addition, the effects of inulin were mimicked by the intake of cholic acid. Strikingly, despite the fact that inulin has been used by the food industry as a sugar and fat replacer in baked and dairy products given its properties of jellification and microcrystal formation,[12] its beneficial effects in human beings remain poorly

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understood.[13,14] Murine studies have claimed that inulin intake, when associated with high-fat or high-sugar diets, can ameliorate or even reverse the development of metabolic syndrome caused by these unbalanced diets.[15–19] On the other hand, detrimental effects of inulin intake also have been reported, mainly at increased doses, leading to the exacerbation of intestinal inflammation in different models of colitis,[20,21] once again highlighting the complexity and context-dependency of such dietary interventions.

Nonetheless, important questions remain when considering both recent articles[6,11] together. How does psyllium contribute to increased bile acid levels in serum? Could psyllium and inulin share the same mechanisms (via bile salt hydrolases) to alter bile acid metabolism in the host, even when showing opposite modulation in the gut microbiome? How can both diets activate the same bile acid–FXR signaling pathway, and yet trigger opposite outcomes in terms of intestinal inflammation? Does the outcome depend on the cell type in which FXR is activated? If so, how is such refinement achieved? Further research along these lines will help to determine the context specificity of distinct dietary fibers. This research is highly relevant to provide a more solid ground to help improve the dietary recommendations to patients with intestinal bowel diseases because for many of them dietary fibers are not always well tolerated, and achieving the right balance between eating or not eating your greens can be a difficult challenge.

RENAN OLIVEIRA CORRÊA, PhD
Q12 Imagine Institute INSERM 1163
Laboratory of Intestinal Immunity
Paris, France

NADINE CERF-BENSUSSAN, MD, PhD
Université Paris Cité
Imagine Institute INSERM 1163
Laboratory of Intestinal Immunity
Paris, France

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Correspondence
Address correspondence to: Nadine Cerf-Bensussan, MD, PhD, INSERM, U1163 Paris, Institute Imagine, Université Paris Descartes Sorbonne Paris Centre, 24 Boulevard du Montparnasse, 75730 Cedex 15, Paris, France. e-mail: nadine.cerf-bensussan@inserm.fr.

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