

## CURRENT UNDERSTANDING OF THE ROLE OF THE GUT MICROBIOME IN HEALTH AND DISEASE AND THE POTENTIAL FOR MICROBIOME-BASED, PERSONALIZED NUTRITION

By Levi Teigen, PhD, RD

### Overview of the gut microbiome

Recent technological advancements allow us to explore, at new depths, the relationship between us as hosts and our intestinal microbes. As discussed by Staley et al.,<sup>1</sup> developing a meaningful understanding of the dynamics of the gut microbiome requires viewing the microbiome as an ecosystem where the microbes interact with, and relate to, one another in complex ways. This approach resists the simple classification of microbes as “good” or “bad”. Furthermore, when understood as a dynamic community, it places an emphasis on moving beyond composition to include measures of functionality. The most common measure of microbial composition utilizes the 16s rRNA amplicon sequencing technique. Approaches to measure the function of the gut microbiome range from shotgun metagenomics, which provides a measure of functional genes, to metabolomics, which is a direct measure of a given metabolite of interest. Investigators studying the gut microbiome often utilize a combination of techniques that incorporate measures of both composition and function.<sup>1</sup>

### Role of the microbiome in health and disease

The gut microbiome is increasingly understood to play an important role in health and disease. It has been implicated in conditions including inflammatory bowel disease,<sup>2</sup> cardiovascular disease,<sup>3</sup> neurodegenerative disorders,<sup>4</sup> and frailty.<sup>5</sup> Additionally, investigators have recently utilized fecal metagenomes to develop the Gut Microbiome Health Index (GMHI), which is being studied for its capacity to independently predict presence of disease based on prevalence of certain microbial species.<sup>6</sup>

Most of our understanding of the health impact of the microbiome comes from cross-sectional observational studies, thus causality cannot be established. However, direct evidence for the role of the microbiome in disease pathogenesis and its role as a therapeutic target is being obtained in a growing list of conditions based on microbiota transplant therapy (MTT) intervention trials.<sup>7-9</sup> The wide application of MTT-based clinical trials only recently became feasible following development of an oral-encapsulated MTT product.<sup>10</sup> As investigators continue to unlock the potential of this therapy, it is reasonable to assume that diet will play a critical role in optimizing outcomes given the impact of diet on nutrient flow to the gut microbes.<sup>11</sup>

## Effect of diet on the microbiome

Diet impacts the composition and function of the microbiome by serving as a source of exogenous substrates for the gut microbiota.<sup>12</sup> Tanes et al. demonstrate the negative effects of altering this nutrient flow with use of a fiber-free diet.<sup>13</sup> Another example of the impact of limiting nutrient flow is observed with exclusive meal replacement shake intake and decreased stability of the microbiome in healthy individuals.<sup>14</sup> Microbiome stability and resilience are 2 important features of microbiome health, where stability is a measure of day-to-day variation and resilience a measure of the ability of the microbiome to recover following a perturbation.<sup>15</sup> In direct contrast to these findings in healthy individuals is the use of exclusive enteral nutrition (EEN) as an effective therapy for Crohn's disease.<sup>16</sup> The mechanism of action of EEN in Crohn's disease has not been fully elucidated, but changes to the microbiome have been hypothesized to contribute to its efficacy.<sup>17</sup> Ultimately, however, these contrasting results underscore the need to develop a deeper understanding of the personalized nature of microbiome response to diet.

The individualized response of the fecal gut microbiota to diet has been shown to occur at the level of both taxonomic composition<sup>14</sup> and function.<sup>18</sup> In some instances, predicting expected response to diet is as simple as whether or not an individual harbors microbes capable of performing specific functions, as seen with methane production.<sup>19</sup> In this instance, the presence or absence of methanogens dictates whether methane can be produced. However, the property of functional redundancy makes it challenging to predict microbiome response to diet as multiple microbes are capable of performing the same function.<sup>20</sup> While this research is still in its early stages, the presence of individualized responses to diet offers an opportunity to one day utilize microbiome characteristics for microbiome-based personalized nutrition recommendations.

## Typical design of and recommendations for designing and conducting diet-microbiome studies in humans

Given the personalized nature of microbiome and diet response, it can be challenging to capture diet-microbiome interactions with traditional cross-sectional study designs. Cross-sectional studies remain a valuable tool in the diet-microbiome space, but they can only identify associations. The complex nature of diet-microbiome interactions requires certain considerations when designing diet-microbiome intervention studies. In fact, because of the importance of trial design in advancing the understanding of diet-microbiome interactions, several reviews have been published on this topic to help improve and advance diet-microbiome research.<sup>21,22</sup> In general, a longitudinal, cross-over study design is preferred due to the individualized nature of diet-microbiome interactions. In addition, timing of dietary intake collection and stool sample collection are of particular importance. In order to optimize timing between dietary intake and stool sample collection, Johnson et al. proposed collection of consecutive days of dietary intake data and stool samples in a staggered and overlapping fashion at relevant timepoints.<sup>21</sup>

Another challenge researchers are working to address is how to best quantify substrate availability (i.e., nutrient flow) to the microbes. Traditionally, nutrient composition of the diet (e.g., grams protein, carbohydrate, fiber) has been used to quantify dietary intake. However, traditional nutrient composition doesn't account for variability in intake of specific foods or the impact of the food matrix on digestibility (i.e., what reaches the colonic microbes).<sup>23</sup> As an alternative to traditional quantification of nutrients in diet-microbiome studies, Johnson et al. developed methodology to utilize food choices, which proved to be a more sensitive measure of diet variability compared to nutrient analysis.<sup>14</sup> This approach may capture food characteristics that are overlooked at the nutrient level, but more work is needed to understand the best approach to quantifying substrate availability to the microbes.

## Conclusion

The gut microbiome is a metabolically active symbiont that is increasingly understood to play an important role in health and disease. Diet serves as a primary source of substrate for the microbes, capable of modifying its composition and function. Response to diet, however, is highly individualized. While this presents a formidable challenge to researchers, it lays the foundation for a future that includes microbiome-based, personalized nutrition.

## ABOUT THE AUTHOR

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# SOY AND THE MICROBIOTA/ MICROBIOME

By **Mark Messina, PhD, MS**

The health effects of soy foods and various soybean components have been widely investigated, although with respect to the latter, most focus has been on protein and isoflavones. A wide range of outcomes has been examined including many chronic diseases in epidemiologic studies and many risk factors for or markers of chronic diseases in clinical studies. One outcome for which a better understanding is needed is the impact of soy on the microbiota/microbiome. Fortunately, several ongoing trials funded by Soy Nutrition Institute (SNI) Global, involving both children and adults, will help address this need.

Perhaps the most obvious way soy may impact the microbiome is via the consumption of fermented soy foods, such as tempeh, miso, and natto. Fermented soy products can contain microbes which may act as a probiotic if these microbes escape digestion in the upper gut. For example, an Indonesian study involving 10 healthy women found that after consuming 100g/d tempeh for 28 days, there was a significant increase in *Bifidobacterium* and *Akkermansia muciniphila* populations, changes which are viewed as potentially beneficial.<sup>1</sup> These results concur with a shorter-term study in humans<sup>2</sup> and animal research.<sup>3,4</sup> An important caveat is that if tempeh is cooked at a high temperature for a long time or pasteurized, the microbes inherent in this product will be killed; although this may not completely eliminate its impact on the microbiome.

Several studies have investigated the effects of both fermented and unfermented soymilk on the microbiota.<sup>5-8</sup> In one study involving healthy men, the relative abundance of *Firmicutes* significantly decreased whereas the relative abundance of *Bacteroidetes* increased in response to 500ml/d soymilk.<sup>7</sup> Correspondingly, the *Firmicutes* to *Bacteroidetes* ratio decreased significantly. Again, these changes are viewed as desirable. However, there were no benefits observed in a study in which infants were fed soy-based infant formula for 1 month after first being fed cow's milk formula.<sup>6</sup> In a Taiwanese study, adults first consumed 250ml fermented or unfermented soymilk twice per day for 2 weeks and then switched to the opposite milk for another 2 weeks.<sup>5</sup> The population of *Lactobacillus* increased in response to unfermented soymilk, but in response to fermented soymilk, the populations of both *Bifidobacterium* spp. and *Lactobacillus* spp. increased as did the ratio of *Bifidobacterium* spp. and *Lactobacillus* spp. to *Clostridium perfringens*. Thus, fermented soymilk outperformed unfermented soymilk. The superiority of fermented vs. unfermented soymilk concurs with the results of a Japanese study.<sup>8</sup>

In terms of soybean components, more than 30 years ago it was shown that soybean oligosaccharides can increase *Bifidobacterium*,<sup>9,10</sup> and for this reason, Japanese researchers suggested using a soybean oligosaccharide extract as a sugar substitute.<sup>10</sup> More recent research in pigs supports the prebiotic effects of soybean oligosaccharides.<sup>11</sup>

It is not surprising that the impact of isoflavones on the microbiota has been studied given the general focus on isoflavones and the known role that the microbiota play in the metabolism of these diphenolic soybean constituents.<sup>12</sup> However, in a Spanish study, 1 month of isoflavone supplementation (80mg/d) increased the relative abundance of the genus *Slackia*,<sup>13</sup> which has been associated with periodontal disease.<sup>14</sup> Even soybean oil has been studied for its effect on the microbiota. For example, a study in mice that intervened with diets containing either olive oil, soybean oil, or coconut oil found that the first 2 oils increased microbial diversity relative to coconut oil.<sup>15</sup>

Finally, numerous studies on the microbiota provide insight into possible differences between plant and animal protein. In a small study involving 23 vegetarians and 23 omnivores, no major differences between dietary groups were observed in terms of fecal bacterial richness, alpha diversity, or beta diversity. However, a minority of potential pathobionts tended to be elevated in omnivores compared to vegetarians, whereas potential probiotic species tended to be higher in the vegetarians.<sup>16</sup> In contrast, a cross-sectional analysis of 2 European cohorts found there was no significant association between protein intake (total, animal, or plant) with either gut microbiota alpha diversity or beta diversity, regardless of ethnicity.<sup>17</sup>

More directly relevant to soy is a randomized, double-blind, parallel-design trial involving 38 overweight individuals who received a 3-week isocaloric supplementation with casein, soy protein, or maltodextrin as a control.<sup>18</sup> The protein supplement was intended to provide 15% of total energy intake at the expense of starch, thus creating a high-protein diet. Although protein supplementation did not alter microbiota composition, it did induce a shift in bacterial metabolism toward amino acid degradation with different metabolite profiles according to the protein source. Casein and soy protein differentially modified the expression of genes playing key roles in homeostatic processes in rectal mucosa, such as cell cycle or cell death.

In summary, soy foods may potentially impact the microbiota/microbiome through multiple components and mechanisms, although at the present time, data are too limited to conclude that any potential changes account for the proposed impact of soy on clinically relevant outcomes. Ongoing research may provide insight as to whether this is the case.

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# FERMENTED FOODS AND SOY

**By Rosanne Rust, MS, RDN**

Have your clients asked about the impact of fermented foods on health? Fermentation is a process by which bacteria break down carbohydrates into alcohol or organic acids. As a result, fermented foods have a slightly distinct and acidic smell to them. Examples of fermented foods and beverages include cheese, sauerkraut, kimchi, kefir, yogurt, kombucha, sourdough bread, stinky tofu, tempeh, miso, and natto. Fermented foods are considered probiotics because they can increase levels of certain bacteria in the gut.

Some evidence suggests fermented soy foods increase the levels of gut bacteria that have been shown to be beneficial to some individuals, including *Bifidobacterium* and *Lactobacillus*. In addition, soybeans and some soy foods contain poorly absorbed oligosaccharides and/or fiber, both of which are fuel for the good bacteria in the gut and support digestive health. Furthermore, fermentation generates bioactive compounds absent in unfermented foods or beverages that may exert health benefits.<sup>1,2,3</sup>

Here's an overview of some fermented soy foods, how they're made, and their good-for-you bacteria:

- **Tempeh** is made by fermenting whole soybeans (whereas tofu is made from soymilk) resulting in a cake-like product. It is a traditional food in Indonesia and has more fiber than tofu and offers a nutty flavor and chewier texture. To make tempeh, soybeans are soaked and cooked, and then inoculated with a mold (often a *Rhizopus* strain) to hasten the fermentation process.
- **Soy sauce** is made by soaking soybeans in a mixture of water, wheat, and salt. This mixture is then naturally fermented with *Aspergillus sojae* and *Aspergillus oryzae* molds.

- **Miso** is a paste produced from fermented soybeans. It is widely associated with Japanese cuisine, but it likely originated in China. It's made from soybeans, salt, and koji (also a strain of *Aspergillus oryzae*) and is used as a seasoning in soups, sauces, or main and side dishes.
- **Stinky tofu** is a fermented tofu that's a popular street food in Taiwan. Like its name suggests, it has a strong, pungent smell. It's made by soaking tofu in a milky brine made with fermented milk and vegetables. Fermentation leads to the production of equol, a metabolite of the isoflavone daidzein, which may have potential health benefits.<sup>4</sup>
- **Natto** is a popular breakfast dish in Japan. The fermented soybeans have a sticky and stringy texture and are often served with rice. To make natto, soybeans are fermented with *Bacillus Subtillis var. natto* bacteria, which produces the enzyme nattokinase. This enzyme exhibits the ability to inhibit blood clots<sup>5</sup> and may help reduce the risk of mortality from cardiovascular disease.<sup>6</sup>

There is a growing body of research suggesting the microorganisms used in the fermentation process, and the fermentation-associated modifications that occur in the food, contribute to a wide range of health benefits. Be sure to educate your clients about the potential benefits of including fermented soy products in their diet.

## ABOUT THE AUTHOR

**Rosanne Rust, MS, RDN**, is an internationally recognized nutrition expert and author who loves food. Her work helps people put food and nutrition into perspective so they can set realistic health goals. She's published several consumer books in the For Dummies® series. Find her on social media @chewthefacts, or visit her website at [www.rustnutrition.com](http://www.rustnutrition.com).

# 3 Ways to Boost Your Gut Health with Soy

The gut plays a pivotal role in your overall health. Not only can a healthy gut support digestive health, but it has also been shown to bolster your immune system<sup>1</sup>, brain health<sup>2</sup> and more. Bacteria found in soy foods, especially fermented soy products, may help promote a healthier gut.<sup>3,4</sup> Check out three easy ways to incorporate more soy foods into your daily routines.

To view, go to: <https://www.soyconnection.com/docs/default-source/infographics/soy-and-gut-health-infographic.pdf>

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