

Soy and Gut Microbiota: Interaction and Implication for Human Health

Haiqiu Huang,[†] Hari B. Krishnan,[§] Quynhchi Pham,[†] Liangli Lucy Yu,[#] and Thomas T. Y. Wang^{*,†}

[†]Diet, Genomics and Immunology Laboratory, U.S. Department of Agriculture—Agricultural Research Service, Beltsville, Maryland 20705, United States

[§]Plant Genetics Research Unit, U.S. Department of Agriculture—Agricultural Research Service, University of Missouri, Columbia, Missouri 65211, United States

[#]Department of Nutrition and Food Science, University of Maryland, College Park, Maryland 20742, United States

ABSTRACT: Soy (*Glycine max*) is a major commodity in the United States, and soy foods are gaining popularity due to their reported health-promoting effects. In the past two decades, soy and soy bioactive components have been studied for their health-promoting/disease-preventing activities and potential mechanisms of action. Recent studies have identified gut microbiota as an important component in the human body ecosystem and possibly a critical modulator of human health. Soy foods' interaction with the gut microbiota may critically influence many aspects of human development, physiology, immunity, and nutrition at different stages of life. This review summarizes current knowledge on the effects of soy foods and soy components on gut microbiota population and composition. It was found, although results vary in different studies, in general, both animal and human studies have shown that consumption of soy foods can increase the levels of bifidobacteria and lactobacilli and alter the ratio between Firmicutes and Bacteroidetes. These changes in microbiota are consistent with reported reductions in pathogenic bacteria populations in the gut, thereby lowering the risk of diseases and leading to beneficial effects on human health.

KEYWORDS: gut microbiota, human health, soy foods, soy components

■ INTRODUCTION

Recent advances in the study of the human microbiota have established its importance in the human body ecosystem and human health. Although there are volumes of literature on the health-promoting effects of soy, soy bioactive components, and their potential mechanisms of action, efforts to understand the role of soy and soy components on human microbiota are just getting started. The aims of this review are (1) to summarize the current knowledge on the effects of soy and soy components on the population and composition of gut microbiota and (2) to bridge the potential beneficial health outcomes associated with altered gut microbiota and consumption of soy. Understanding the role of soy and its components in influencing and modulating gut microbiota provide a critical piece of information to further our knowledge of the potential mechanism of action of soy's bioactive components and science-based information to promote the use of soy as a functional food.

■ SOY AS AN EMERGING FOOD IN THE UNITED STATES

The United States is the world's leading producer of soy.¹ In 2013, the United States accounted for >30% of world soy production.² As a food, soy consumption has historically been associated with Asian countries, such as China and Japan, rather than the United States.³ However, the popularity of soy foods in the United States increased significantly after a 1999 decision by the Food and Drug Administration to allow soy-food labels to display the health claim that soy protein may reduce the risk of heart disease.⁴ The U.S. retail soy food industry grew from \$1 billion in 1996 to \$4.5 billion in 2013. In 2014, a survey by

the United Soybean Board showed that approximately three-fourths of the U.S. population reported to have consumed soy foods or beverages, and about one-third of Americans consume soy food products at least once a week.⁵ Consumer awareness of soy's nutritional/health-promoting value appeared to fuel the increased demand for soy, as 26% of consumers indicated that they specifically chose soy foods because of the health benefits.^{6–8} Therefore, science-based information on the health-promoting effects of soy and soy components will have significant economical and societal impact in the United States.

■ SOY FOODS PROMOTE HUMAN HEALTH

Epidemiological and experimental studies supporting the health benefits of soy and soy foods include the ability to protect against cardiovascular diseases,^{9–11} mitigate obesity, diabetes,¹² and related complications,^{13,14} reduce risk of certain types of cancer, such as breast and prostate cancer,^{15–18} and potentially benefit cognitive function and immune function^{19–21} and other chronic diseases.^{3,22} For example, prospective observational studies in the Asian population showed a reduction of total cholesterol and low-density lipoprotein (LDL), as well as ischemic and cerebrovascular events, when consuming a daily amount of 6 g or more of soy protein.²³ In addition, a meta-analysis of 38 controlled clinical trials that evaluated the correlation between consumption of soy and lipid levels showed that consumption of an average of 47 g of soy protein

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per day resulted in significant decreases of total cholesterol (9.3%), low-density lipoprotein (LDL) cholesterol (12.9%), and triglycerides (10.5%).²⁴ Moreover, soy isoflavones were shown to be bioactive and may help improve circulation by exerting vasodilatory and antioxidant effects in cerebral arteries, modulating vascular reactivity through the activation of estrogen receptors, and/or intracellular kinase signaling cascades.^{25,26} Soy was reported to alleviate obesity-related complications by regulating adipogenesis via decreasing lipoprotein lipase activity and improving insulin resistance.^{12,14} Soy consumption is also associated with prevention of certain types of cancer, such as breast, prostate, and colon cancers,^{15–17} and such effects are largely attributed to soy isoflavones, which have been shown to modulate cell cycle, apoptosis, differentiation, proliferation, growth, and cell signaling.^{27–29}

Despite extensive studies on the health benefits of soy, the complexity of soy components makes it difficult to dissect out the precise active component(s) or compound(s) responsible for a particular health-promoting effect and specific bioactivity. Validating additional biological target(s) and elucidating the mechanism of action exerted by soy and its components are warranted to fully realize the health-promoting effects of soy.

HUMAN GUT MICROBIOTA

Joshua Lederberg in a 2001 paper defined the microbiota as “the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space”.³⁰ The human gut microbiota is composed of a variety of microorganisms including bacteria, fungi, and archaea. The most recent calculation of bacterial cells' number in human microbiota estimated a comparable number between the microbiota and human cells,³¹ much less than that of previous studies indicating there are 10 times more bacterial cells than human cells.^{32,33} Furthermore, the total number of genes in the human microbiota is estimated to far exceed the number of human genes by at least 100 times,³⁴ which creates a very large and complex ecosystem between the human body and the residing microorganisms.

It was estimated that 300–500 different species of bacteria make up the majority of microorganisms in the human gut.³⁵ The Bacteroidetes (contains genera *Bacteroides* and *Prevotella*) and the Firmicutes (contains genera *Clostridium*, *Eubacterium*, and *Ruminococcus*) are the predominant phyla in the human gut, which account for >90% of the microbiota population.^{34,36–38} Actinobacteria, Proteobacteria, Fusobacteria, Spirochaetes, Verrucomicrobia, and Lentisphaerae are also present but in lower proportions (Figure 1).^{36,39} Recent research suggested that no bacterial species were shared among all human gut microbiota examined, and the high levels of functional redundancy among bacteria may have rendered “core” species unnecessary.⁴⁰ However, a “core” collection of genes does exist, serving as the basis of “core” functional components.^{40,41}

GUT MICROBIOTA AND HUMAN HEALTH

The interaction between bacteria and human cells is crucial to the protective role of intestinal commensal bacteria for the maintenance of health.⁴² Microbiota have been shown to play an important role in appetite control, energy balance, immune function, allergies, behavioral perturbations, and pathology or prevention of metabolic diseases, such as obesity, diabetes, cancers, and cardiovascular diseases.^{43–45} Clinical trials and

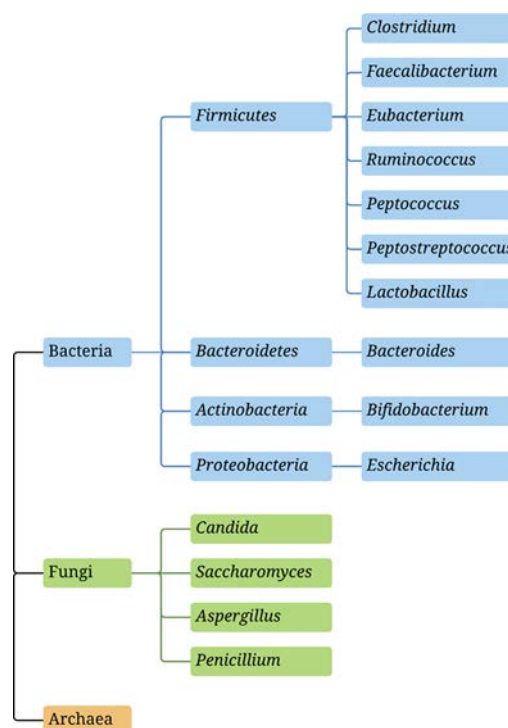


Figure 1. Major bacteria, fungi, and archaea found in the human gut.

comparisons of intestinal microbiota between diseased and healthy subjects have identified inflammation-related biomarkers that are associated with functional microbiota changes.⁴⁶ Table 1 summarizes the relationship between the microbiota and human health. Although the exact influence and mechanisms remain unknown, the human microbiota appeared to exert a broad range of health-related effects in human development, physiology, immunity, and nutrition.⁴⁷

FACTORS INFLUENCING GUT MICROBIOTA COMPOSITION

Many factors appeared to influence gut microbiota composition, which included but were not limited to host genotypes, health condition, lifestyle, medication (e.g., antibiotics), and diet.^{48,49} The host genetic background plays an important role in the composition of the gut microbiota. Higher similarity of the gut microbiota was observed among relatives than among unrelated individuals.^{40,50,51} In mouse models, a relationship exists between 18 host quantitative genetic trait loci to the relative abundances of specific microbial taxa in the four dominant phyla, Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria.⁵² Also, specific mutations in host genes can significantly shift bacterial community structure. For example, patients with familial Mediterranean fever (MEFV) exhibit single-nucleotide polymorphism (SNP) at the MEFV gene locus encoding pyrin, and the mutation at this locus is associated with a decrease in the total number of bacteria, lower bacteria diversity, and major changes in bacterial populations within the Bacteroidetes, Firmicutes, and Proteobacteria phyla.⁵³ Apolipoprotein I (Apoa-I) knockout mouse was reported to exhibit a different microbiota structure from its wild-type counterpart.⁵⁴ Several other genes have been identified to correlate with altered microbiota abundance and composition, which include leptin,^{37,55} myeloid differentiation primary response 88 (MyD88),^{56,57} Toll-like receptor

Table 1. Potential Impact of Microbiota on Human Diseases and Conditions

condition	potentially affected physiological event	references
obesity	energy harvest and adiposity	44, 76, 91
metabolic syndrome/diabetes	control of glucose homeostasis and insulin resistance	54, 57, 59, 159–161
systemic inflammation	intestinal permeability and endotoxemia	162–164
rheumatoid arthritis	chronic inflammation and autoimmune activation	158, 165, 166
asthma	regulation of immune system (T cells and cytokines)	167–169
cardiovascular diseases	metabolism of dietary components and energy harvest	170–173
nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH)	energy homeostasis, intestinal permeability, endotoxin translocation, and cytokine production	174–178
hypertension	energy expenditure, metabolism of nutrients, ion transport, and fatty acid production	179–182
cancers (colorectal and liver)	pro-carcinogenic metabolites, gastrointestinal inflammation	183–187
inflammatory bowel disease (IBD)/irritable bowel syndrome (IBS)/Crohn's disease	dysregulation of immune response, inflammation and cytokine production	188–191

(TLR),^{58,59} nucleotide-binding oligomerization domain (NOD),^{60,61} immunoglobulin (Ig) A,^{62,63} and interferon (IFN)⁶⁴ genes.

Health status is another key factor that affects gut microbiota structure. Patients with health conditions in the gastrointestinal (GI) tract were shown to harbor microbiota distinct from their healthy counterparts. Inflammatory bowel disease (IBD) was shown to reduce bacteria in the Bacteroidetes and Firmicutes phyla and shift the bacterial population toward the Proteobacteria and Actinobacteria phyla.⁶⁵ Diseases not originating from the GI tract can also have an impact on gut microbiota. Type 2 diabetes patients were shown to have fewer bacteria from the Firmicutes phylum and an increased proportion of bacteria from the Bacteroidetes phylum.⁶⁶ Lifestyle, such as levels of exercise⁶⁷ and hygiene habits,^{68,69} was also shown in previous research to influence the composition of gut microbiota. It has been reported that exercise shifts the gut microbiota profile and increases butyrate-producing bacteria,⁶⁷ and a high-hygiene environment was shown to interfere with the natural stabilization of the gut microbiota.⁶⁹ In addition, the use of antibiotics can have both acute and long-term consequences in the composition of the gut microbiota.^{70–73} Perturbation of the gut microbiota is signified by the loss of diversity and a shift in community composition during the antibiotic treatment, and a return to normal condition after cessation of antibiotic treatment is not guaranteed.^{70,71} Repeated or long-term use of antibiotics poses additional concerns of selective pressure giving rise to resistant bacteria and resistance genes, which may exert a long-lasting effect on the composition and function of gut microbiota.⁷²

■ RELATIONSHIP BETWEEN DIET AND GUT MICROBIOTA

Diet, both long-term and short-term exposure, has emerged as the major factor in shaping the gut microbiota and, in some cases, appeared to be more important than the host genetics.^{74,75} As mentioned above, knockout of the ApoA-I gene can lead to altered microbiota in a mouse model. However, missing ApoA-I accounted for only about 12% of the microbiota change when compared to the diet composition changes, which can account for 57% of changes in the microbiota.⁵⁴ Low-calorie diets via either fat or carbohydrate restriction resulted in an increase in Bacteroidetes.^{76,77} Diets composed of animal or plant constituents were found to differentially alter the Firmicutes/Actinobacteria to Bacteroidetes ratio.^{40,76,78} An animal-based diet preferentially promotes

the abundance of Bacteroidetes (such as *Alistipes* and *Bacteroides*) and reduces Firmicutes (such as *Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii*) as early as 2 days into the dietary intervention.⁷⁵ On the other hand, consumption of a plant-based diet rich in dietary fiber results in an increase of Firmicutes, such as *Ruminococcus bromii* and *Eubacterium rectale*.⁷⁹ Diet's effect on the gut microbiota can also be observed in the very early stage of life. Several studies have shown more bifidobacteria in the gut microbiota in breast-fed infants than those fed with formula.^{80–83} Long-term consumption of a diet rich in carbohydrates, fiber, and nonanimal protein is associated with higher levels of *Prevotella* and lower levels of *Bacteroides* compared to a diet high in animal protein, sugar, starch, and fat and low in fiber.^{84,85} The fat content in a diet was also found to alter the composition of the microbiota, and the gut microbiota changes rapidly in animals when switched from low-fat to high-fat diets.^{78,86} A high-fat diet was shown to induce an increase in *Lactobacillus*, and *Lactobacillus* is also involved in simple sugar degradation.^{87–89} *Ruminococcus* and *Prevotella* were shown to be involved in polysaccharide metabolism, especially fiber, in the gastrointestinal tract.^{79,90} Enterobacteriaceae, *Akkermansia*, and bifidobacteria have been shown to be involved in energy metabolism and balance, and an increase in carbohydrate intake was shown to elevate Enterobacteriaceae and bifidobacteria population, whereas the *Akkermansia* population was negatively associated with consumption of polysaccharides.^{56,86,91–93} Bifidobacteria population was also shown to correlate positively with cholesterol intake and metabolism.⁹⁴ Hence, the gut microbiota might be able to serve as an indicator of long-term and short-term dietary patterns.

■ EFFECT OF SOY FOODS ON GUT MICROBIOTA

Several recent studies have reported that the consumption of soy or soy foods may alter the composition and population of the gut microbiota (see Table 2).^{95–97} Soy and soy foods can provide nutrients and energy that preferentially support the growth of some gut bacteria.^{95,98,99} For example, soy milk is one of the most consumed soy foods in both the United States and traditional soy-consuming Asian nations.^{100,101} In soy milk, 24% of calories are from protein, such as glycinin and β -conglycinin, 45% from carbohydrate, including raffinose, stachyose, sucrose, fructose, glucose, galactose, and other mono- and oligosaccharides, and 31% from oil.^{102,103} These nutrients can be utilized by certain gut bacteria and shift the composition of the gut microbiota. Fernandez-Raudales and

Table 2. Effects of Soy and Soy Foods on the Gut Microbiota

experimental model/subject	soy foods or components	amount/dosage	duration	change in microbiota		reference
				increase	decrease	
human (3–8 months old, male and female, $n = 12$, cow's-milk protein hypersensitive)	soy milk	N/A ^a	1 month	no change		Piacentini et al., 2010 ¹⁰⁴
human ($n = 28$)	regular soy milk fermented soy milk	500 mL/day	2 weeks	<i>Lactobacillus</i> <i>Bifidobacterium</i> <i>Lactobacillus</i>	<i>Clostridium</i>	Cheng et al., 2005 ¹⁰⁹
human (menopausal women, age 48–61 years, $n = 16$)	soy isoflavone concentrate	80 mg/day	6 months	no change		Guadamuro et al., 2015 ¹³⁶
human (menopausal women, age 60.4 ± 7.1 years, $n = 39$)	soy isoflavones	100 mg	2 months	<i>Bifidobacterium</i> <i>Clostridium</i> <i>Enterococcus</i> <i>Eubacterium</i> <i>Faecalibacterium</i> <i>Lactobacillus</i>		Clavel et al., 2005 ¹³⁴
human (6 males and 4 females, age 21–25 years)	nonfermented soybean milk fermented soybean milk	100 g/day	2 weeks	bifidobacteria lactobacilli	no change <i>Clostridia</i>	Inoguchi et al., 2012 ⁹⁹
human (overweight, male, $n = 64$)	conventional soy milk (26.5% β -conglycinin/ 38.7% glycinin) low glycinin soy milk (49.5% β -conglycinin/ 6% glycinin)	500 mL/day	3 months	total bacteria Bacteroidetes proteobacteria total bacteria Bacteroidetes <i>Faecalibacterium</i> Proteobacteria	<i>Bifidobacterium</i> Firmicutes <i>Lactobacillus</i> <i>Bifidobacterium</i> Firmicutes <i>Lactobacillus</i>	Fernandez-Raudales et al., 2012 ⁹⁵
Sprague–Dawley rat (5 weeks old, male, $n = 30$)	soy milk (powder)	12% w/w ^b	6 weeks	<i>Allobaculum</i> <i>Coprococcus</i> <i>Lactobacillus</i> <i>Parabacteroides</i>	<i>Akkermansia</i> <i>Alistipes</i> <i>Barnesiella</i> <i>Butyrivimonas</i> <i>Clostridium</i> <i>Ruminococcus</i>	Lee et al., 2015 ¹⁰⁶
Wistar rat (SPF, 8 weeks old, $n = 60$)	soy milk	3 mL/kg of BW/day	30 days	total aerobes total anaerobes Enterobacteria <i>Enterococcus</i> <i>Lactobacillus</i> total anaerobes	<i>Bacteroides</i> <i>Bifidobacterium</i> <i>Clostridium</i>	Bedani et al., 2010 ¹⁰⁵
	fermented soy milk (by <i>Enterococcus faecium</i>)				<i>Bacteroides</i>	

Table 2. continued

experimental model/subject	soy foods or components	amount/dosage	duration	change in microbiota		reference
				increase	decrease	
Wistar rat (<i>n</i> = 40)	soy milk fermented soy milk (by <i>Lactobacillus plantarum</i>)	2 mL/animal	4 weeks	<i>Bifidobacterium</i> <i>Clostridium</i> <i>Enterococcus</i> <i>Lactobacillus</i>	no change <i>Clostridium</i>	Wang et al., 2013 ¹⁵⁰
Wistar Hannover rat (12 weeks old, female, <i>n</i> = 30)	tofu diet	N/A	30 days	lactic acid producing bacteria	Enterobacteriaceae	Arroyo et al., 2005 ¹⁰⁷
Wistar rat (4 weeks old, male, <i>n</i> = 6)	soy protein	20% w/w	16 days	<i>Enterococcus</i>	lactobacilli <i>Ruminococcus</i>	An et al., 2014 ¹¹⁶
C57BL/6J mice (male, <i>n</i> = 10)	freeze-dried doenjang	5% w/w	7 days	<i>Bacteroidetes</i> bifidobacteria <i>Odoribacter</i>	<i>Clostridium</i> Enterobacteriaceae Firmicutes Lachnospiraceae <i>Pseudoflavonifractor</i> Ruminococaceae	Jang et al., 2014 ¹¹¹
BALB/c mice (male, 7–8 weeks old, <i>n</i> = 36)	okara (soy pulp/soy fiber)	0.3 g/kg BW/day	28 days	<i>Bifidobacterium</i> lactobacilli	<i>Escherichia coli</i>	Li et al., 2013 ¹¹⁰
BALB/c mouse (adult, male, <i>n</i> = 40)	deshipu stachyose granules	0.42, 0.83, 2.49 g/kg BW/day	14 days	bifidobacteria lactobacilli	bacilli	Li et al., 2013 ⁹⁸
C57Bl/6NTac (male, <i>n</i> = 20)	activated soy pod fiber (47.9% carbohydrates, 30% protein, 13.4% fat, with 175 µg/g glyceollin)	15% w/w	16 days	<i>Alistipes</i> <i>Bacteroides</i> <i>Barnesiella</i>	<i>Akkermansia</i> <i>Lactococcus</i> <i>Ruminococcus</i> <i>Parabacteroides</i>	Boue et al., 2016 ¹³⁰
New Zealand white rabbit (male, 8–9 weeks old, <i>n</i> = 30)	aqueous soy extract	2.8 mL/kg BW/day	60 days	<i>Bifidobacterium</i> <i>Clostridium</i> enterobacteria <i>Enterococcus</i> <i>Lactobacillus</i> <i>Bifidobacterium</i> <i>Clostridium</i> <i>Enterococcus</i>	Enterobacteria	Cavallini et al., 2011 ¹¹²
	fermented aqueous soy extract (by <i>Enterococcus faecium</i> and <i>Lactobacillus helveticus</i>)					

Table 2. continued

experimental model/subject	soy foods or components	amount/dosage	duration	change in microbiota		reference
				increase	decrease	
Golden Syrian hamsters (male, 6–8 weeks old, $n = 32$)	soy protein concentrate (SPC)	27% w/w	6 weeks	Bifidobacteriaceae <i>Lactobacillus</i>	Bacteroidaceae	Butteiger et al., 2016 ⁸⁶
	partially hydrolyzed soy protein isolate	24% w/w		<i>Clostridiales</i> spp.	Porphyromonadaceae	
	intact soy protein isolate	24% w/w		Deferribacteraceae Lachnospiraceae		
Czech Fleckvieh × Holstein cows (female, $n = 12$)	soy isoflavones (daidzein, genistein, glycitein)	12.5 g of 40% isoflavone extract	14 days	Bifidobacteriaceae Firmicutes Lactobacillales Planctomycetes	Bacteroidetes Fibrobacteres Proteobacteria Verrucomicrobia	Kasparovska et al., 2016 ¹³⁵
	soybean oil	4% w/w	21 days		<i>Ruminococcus albus</i> <i>Fibrobacter succinogenes</i>	Yang et al., 2009 ¹⁴³
Arctic charr (<i>Salvelinus alpinus</i> L., $n = 5$)	soybean oil marine oil	18%	N/A	<i>Acinetobacter</i> <i>Moraxella</i> <i>Pseudomonas</i> <i>Carnobacterium</i>	<i>Aeromonas hydrophila</i> <i>Cytophaga-Flexibacter</i> <i>Micrococcus</i>	Ringø et al., 2002 ¹⁹²

^aN/A, not mentioned in the reference. ^bw/w percentage of weight of supplementation in diet.

colleagues examined the effect of the consumption of soy milk on the gut microbiota in overweight and obese men and found an increase in total gut bacteria from soy milk (500 mL) supplement. Soy milk consumption also changed the bacterial composition, which led to reductions in the relative abundance of bifidobacteria and Firmicutes and increases in the abundance of Bacteroidetes and Proteobacteria.⁹⁵ This shift in the Firmicutes to Bacteroidetes ratio has been reported to be associated with beneficial health outcomes, including reduced risk of obesity and other metabolic syndromes.^{56,74} The effects of soy milk may be time- and/or growth stage-dependent in humans. Piacentini et al. fed infants (3–8 months old) with soy milk in place of their bovine milk-based formula for 1 month and found no variation in selected bifidobacteria species, *Ruminococcus* species, and the *Bacteroides* genus.¹⁰⁴ Studies of soy milk in animal models revealed specific changes in some phyla and genera. In a Wistar rat model, feeding of soy milk induced significant increases in total aerobes, total anaerobes, *Enterococcus*, *Lactobacillus*, and *Enterobacter* and decreases in *Clostridium*, *Bacteroides*, and *Bifidobacterium*.¹⁰⁵ Lee and colleagues found supplementation of 12% (w/w) soy milk powder in a Sprague–Dawley rat model on a high-cholesterol diet induced an increase in the Firmicutes (*Coprococcus*, *Lactobacillus*, *Blautia* genera) to Bacteroidetes (*Barnesiella* genus) ratio.¹⁰⁶ The authors concluded that diets containing soy milk and fiber mixtures rescued cholesterol-disturbed gut microbiota, which limits cholesterol-induced colonic inflammation.¹⁰⁶

Other soy foods have also been found to alter the gut microbiota (see Table 2). Tofu, a popular food in Asian cuisine, is a good source of protein. Moreover, tofu can also provide both pre- and pro-biotics.¹⁰⁷ Arroyo and colleagues found that after a 30 day feeding of a tofu diet, an increase in gut lactic acid producing bacteria and a decrease in enterobacteria in a rat model were observed.¹⁰⁷ Soy oligosaccharides (mainly stachyose and raffinose) in the tofu can be utilized by lactic acid producing bacteria and bifidobacteria.¹⁰⁸ These bacteria are known to compete with and inhibit the growth of potential pathogens such as Enterobacteriaceae.^{107,108} Tofu can also act as a probiotic. *Bacillus*, *Enterococcus*, *Streptococcus*, lactobacilli, and bifidobacteria are some of the most commonly found microorganisms in tofu,¹⁰⁷ which adds another dimension to studying soy's health-promoting effect.

Overall, recent studies suggest that soy-based diets can increase the population of the “good” bacteria, such as lactobacilli and bifidobacteria,^{106,109,110} while decreasing the number of “bad” bacteria, such as enterobacteria,^{107,111,112} in the gut microbiota. Such changes may contribute to soy foods' ability to reduce the risk of metabolic syndromes, inhibiting the population of pathogenic bacteria in the gut, and improving immune function and inflammatory status in the circulation.^{76,113} However, discrepancy in the effects of soy foods among the studies existed and may stem from (1) differences in the preparation of soy milk, which were usually not specified; (2) differences in baseline gut microbiota compositions between the subjects (adult men vs infants); (3) age, gender, and ethnic differences among the subjects; or (4) amount consumed. Future studies taking into consideration these variables are warranted to confirm/validate the effects of soy foods on the gut microbiota.

■ EFFECT OF SOY BIOACTIVE COMPONENTS ON THE GUT MICROBIOTA

Efforts have also been made to elucidate the precise components in soy that may contribute to modulation of the gut microbiota (see Table 2).

Soy Protein. Soy protein can serve as nitrogen and energy sources for bacteria, which support their growth and maintenance in the gut.^{114,115} An and colleagues observed a shift of bacteria composition in the Firmicutes phylum, specifically an increase in the abundance level of *Enterococcus* and decreased levels of *Ruminococcus* and lactobacilli, after 16 days of supplementation of 20% soy protein in a Wistar rat model.¹¹⁶ Butteiger and colleagues supplemented soy protein concentrates in a Western style diet for 3 weeks and observed significant increases in Bifidobacteriaceae, Clostridiales, and Deferribacteraceae and decreases in Bacteroidetes (Bacteroidaceae and Porphyromonadaceae) in a Golden Syrian hamster model.⁹⁶ The major bacteria that can metabolize protein in the gut are *Clostridium* and *Bacteroides*.¹¹⁷ Differential changes of bacteria in *Clostridium* and *Bacteroides* genera upon soy protein consumption may indicate a complex interaction between soy protein and gut bacteria, as well as among the bacteria in the gut. Additionally, specific soy proteins were shown to shift the gut bacteria composition. Significantly higher levels of *Bacteroides* and *Prevotella* were observed in individuals consuming soy milk containing 49.5% β -conglycinin and 6% glycinin comparing to those consuming soy milk with 26.5% β -conglycinin and 38.7% glycinin,⁹⁵ indicating that a higher β -conglycinin to glycinin ratio in protein content may preferentially promote the growth of bacteria in the Bacteroidetes phylum. Hence, the existing studies support the role of soy protein in modulating gut bacteria, mainly in the phyla of Firmicutes and Bacteroidetes. However, there is currently no consensus on specific changes of gut microbiota by soy protein. The discrepancy in the literature may result from the different baseline composition of the gut microbiota, characteristic of proteins, availability of other nutrients, such as carbohydrates, and animal models used.^{114,118} Further elucidating the relationship between soy protein and microbiota would be critical, as soy protein contains all of the essential amino acids for human nutrition and is gaining popularity in the food industry and marketplace as a nutritional food ingredient or dietary supplement.⁹

Soy Oligosaccharides and Fiber. Soy oligosaccharides and fiber are known to possess prebiotic properties.¹⁰⁸ Soy oligosaccharides can reach the colon intact without being digested.¹¹⁹ In an in vitro study, bifidobacteria and lactobacilli were shown to metabolize the soy oligosaccharides stachyose and raffinose, whereas other enteric bacteria only minimally utilized these saccharides.^{120,121} Li and colleagues confirmed in vivo that supplementation with as low as 0.83 g of stachyose/kg body weight (BW) in BALB/c mice led to increases in the levels of bifidobacteria and lactobacilli and a decrease in enteric bacilli level.⁹⁸ Although dietary fiber's effects on gut microbiota have been widely studied and reviewed,¹²² specific studies on soy fiber and gut microbiota are rare in the literature. Soy fiber is primarily composed of pectic polysaccharides.¹²³ Pectic polysaccharides were shown to affect the abundance of *Bacteroides* in the gut; however, the direction of changes varied in different studies,^{124,125} indicating that the molecular composition as well as linkage structures of dietary fibers may alter their effect on the gut microbiota. Additionally, soy fiber

has been reported to alter the level of short-chain fatty acids such as butyrate,^{126,127} which are the main byproducts of the fermentation of nonstarch polysaccharides by the anaerobic microbiota in the gut.^{128,129} Therefore, supplementation of soy fiber may affect the population and composition of these bacteria. Recently, Li and colleagues observed in BALB/c mice supplemented with 0.3 g/kg BW of purified okara (soy pulp) dietary fiber resulted in increases in bifidobacteria and lactobacilli and a decrease in *Escherichia coli*.¹¹⁰ Soy pod fiber is another component that could exert prebiotic effects and promote a shift in the gut microbiota. Boue and colleagues showed that supplementing 15% activated soy pod fiber for 16 days resulted in significant increases in *Bacteroides*, *Flavonifractor*, *Barnesiella*, *Oscillibacter*, and *Alistipes* and significant decreases in the abundance of *Ruminococcus*, *Lactococcus*, *Akkermansia*, *Hydrogenoanaerobacterium*, and *Parabacteroides*.¹³⁰ Hence, increasing evidence supported that oligosaccharides and fiber may contribute to soy and soy foods' overall effects on the gut microbiota. However, specific soy components that contributed to specific changes in the gut microbiota and the correlation of such changes with health-promoting efficacies warrant further study.

Isoflavones. Isoflavones are naturally produced by plants to deter bacterial and fungal infection and, therefore, likely to also possess antibacterial activities toward gut bacteria.^{131,132} Although the beneficial effects of isoflavones have been well studied,^{10,14,20,133} their direct effect on the gut microbiota is less clear. A study of 17 postmenopausal women showed that the gut microbiota changed significantly after 1 week of supplementation with soy isoflavones. Subjects in this study were given a soy bar containing 160 mg of soy isoflavones (including genistein, daidzein, and glycitein) and 1 g of saponin.⁹⁷ Proportions of bifidobacteria in the gut microbiota significantly increased and lactobacilli decreased in all subjects after soy isoflavone supplementation, and the increases in levels of bifidobacteria and eubacteria were more pronounced in equol-producing individuals than in nonproducers.⁹⁷ A similar observation was also reported in another study that involved 39 postmenopausal women receiving 100 mg per day of soy isoflavones for 2 months.¹³⁴ Increases in *Clostridium*, *Eubacterium*, *Lactobacillus*, *Enterococcus*, *Faecalibacterium*, and *Bifidobacterium* were observed with isoflavone supplementation, with equol producers ($n = 12$) having enhanced increases in *Clostridium* and *Eubacterium*.¹³⁴ Such similar increases in Firmicutes were also observed in a cow model fed soy isoflavones.¹³⁵ However, a study with 16 menopausal women supplemented with 80 mg soy isoflavone concentrate per day showed no effect on the gut microbiota,¹³⁶ indicating that soy isoflavones' effect on gut microbiota may be dose-dependent as well as subject-dependent.

Soy phytochemicals, including the isoflavones, undergo hydrolysis in the upper gastrointestinal tract and are metabolized to smaller metabolites, such as phenolic acids and short-chain fatty acids, in the colon, where most of the phytochemicals (up to 90%) are absorbed and utilized.^{43,137} It has been reported that individual differences in the composition of gut microbiota can influence the metabolism of polyphenols.^{43,137} The gut microbiota is known to differentially metabolize the major soy isoflavones, genistein and daidzein, and the conversion of daidzein to equol has been shown to have an impact on human health, such as cancer risk.^{138,139} The bidirectional interactions between the gut microbiota and soy isoflavones render the causal relationship of soy isoflavones on

gut microbiota difficult to determine in supplementation studies with recruited volunteers. Further studies using gnotobiotic animal models transplanted with microbiota from different donors may help to clarify the influence of soy isoflavones on the structure of the gut microbiota.

Soybean Oil. Soybean oil is one of the most produced and widely consumed cooking oils in the world.¹⁴⁰ The major fatty acids in soybean oil are linoleic acid (54%), oleic acid (24%), and palmitic acid (11%).¹⁴¹ Although soybean oil is widely used in animal feed, studies on the effect of soybean oil on gut microbiota are rare in the literature. The main group of bacteria affected by soybean oil consumption was Proteobacteria, as well as genera in Firmicutes and Bacteroidetes.^{142,143} Using soybean oil (18%) instead of marine oil in Arctic charr feed induced a shift in gut Proteobacteria (increases in *Acinetobacter*, *Moraxella*, and *Pseudomonas* and a decrease in *Aeromonas*).¹⁴² Another study by Yang et al. showed that supplementation of 4% soybean oil in cow feed led to significant decreases in *Ruminococcus* and *Fibrobacter*.¹⁴³ Because of the prevalence of soybean oil in our food, more studies are warranted to validate the effects of soybean oil on gut microbiota.

Overall, the current literature supported soy components' role in changing gut microbiota composition. However, work remains to elucidate and validate specific changes affected by soy bioactives as well as what beneficial effects such changes would elicit.

■ EFFECT OF FERMENTED SOY FOODS ON GUT MICROBIOTA

Traditionally, many soy foods consumed are fermented, such as fermented soy milk (yogurt), fermented tofu, soy paste, and soy sauce.³ Fermented soy foods have been shown to possess health-promoting effects, such as antiobesity, anti-inflammation, improving gastrointestinal tract health and the immune system, and reducing the risk of certain cancers.^{144–147} The fermentation process not only affects a food's sensory properties and shelf life but also changes its nutritional value and improves digestibility.¹⁴⁸ More importantly, microorganisms such as bacteria, yeasts, or both are usually used in food fermentation, making fermented soy foods a good source of both pre- and probiotics.^{147,149} Similar effects on increases in bifidobacteria and lactobacilli could be induced by both regular and fermented soy milks, with fermented soy milk showing an enhanced effect.^{109,112} Presumably, the enhanced effects are derived from the probiotic in the fermented soy milk. Fermented soy foods, using bacteria species of lactobacilli and *Enterococcus*, were shown to help increase these bacteria in the gut (see Table 2).^{105,112,150} Aqueous extracts of soy fermented with *Enterococcus faecium* and *Lactobacillus helveticus* were shown to significantly increase *Enterococcus*, lactobacilli, and bifidobacteria populations and decrease the level of enterobacteria genera in the gut.¹¹² Soy milk fermented by *Enterococcus faecium* or *Lactobacillus plantarum* significantly induced the abundance of *Enterococcus*, *Lactobacillus*, bifidobacteria in the gut, whereas differential effects were observed in gut *Clostridium* and *Bacteroides*.^{105,150} Therefore, on the basis of the existing literature, fermented soy foods exert both pre- and probiotic effects on the gut microbiota. Future studies are needed to elucidate the health-promoting effect resulting from the effects of specific soy fermentation product(s) on the gut microbiota.

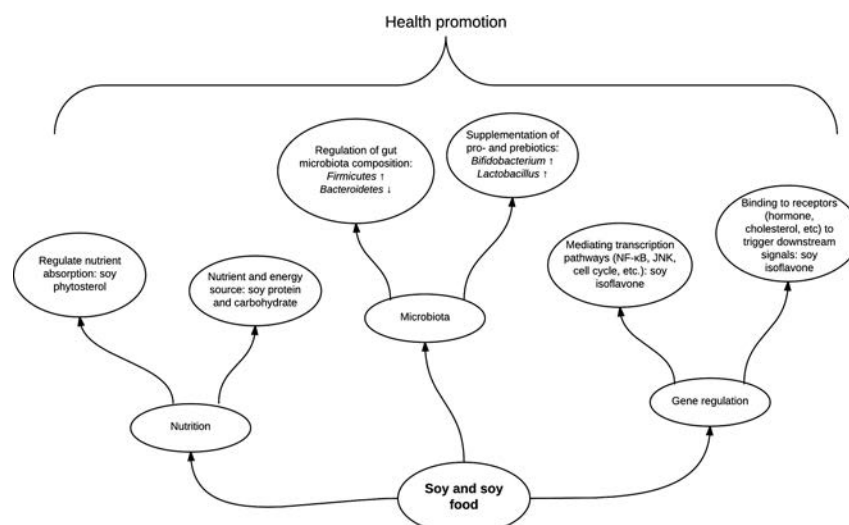


Figure 2. Schematic diagram of potential mechanism for health effects of soy and soy foods.

■ FUTURE DIRECTIONS

In this review, we attempt to summarize the current knowledge of the effects of soy foods and soy bioactive components on the gut microbiota. On the basis of the existing literature, it is apparent that soy or soy foods can modulate gut microbiota. In most cases, the shift in gut microbiota composition, such as increases in probiotics (lactobacilli and bifidobacteria) and the Firmicutes to Bacteroidetes ratio, favors a health-promoting role of soy and soy foods. [Figure 2](#) summarizes the documented effect of soy/soy foods on the microbiota and their biological outcomes in the literature. However, several critical issues need to be addressed for potential future direction.

(1) Choice of Animal Models. Different animal models were used in various published studies. Previous studies have reported that distinct baseline gut microbiota were found in different animal models.¹⁵¹ Studies have been conducted in different mouse (C57BL/6J, BALB/c, et al.)^{110,111} and rat (Sprague–Dawley, Wistar et al.) models.^{105,106} Differences in genetic backgrounds, along with the different feeding methods and periods, may contribute to the different outcomes observed in the microbiota changes. Future studies using defined microbiota (gnotobiotic) models or analyzing the baseline gut microbiota in addition to the changes after supplementation may help clarify the discrepancies between animal models, as well as to correlate the changes observed to the baseline composition of gut microbiota.

(2) Human Subjects. Compared to studies in model animals, which are usually given defined diet and standardized living condition, several factors further confound the causal relationship between soy and soy food consumption and gut microbiota changes, such as diet, genetic background, use of antibiotics, and lifestyle.^{48,49} The human gut microbiota is known to differ greatly among individuals and stages of life,^{152,153} and distinct effects of soy and soy foods on the gut microbiota were reported in different cohorts.^{95,104,109} Therefore, it is important to take into consideration all of these factors in the design of studies, such as baseline diet and use of antibiotics, as well as the baseline gut microbiota, which will help better interpret the reported observations and facilitate the elucidation of soy's effect on gut microbiota across different studies.

(3) Differences in Soy Food Preparation and Composition. Lack of adequate information on the preparation procedure of soy foods (such as soy milk^{99,104,105,150}) or the composition of soy components (such as soy protein^{96,116}) makes it difficult to correlate the changes in microbiota to specific compound(s) in soy. Future studies should consider characterizing the nutrient and phytochemical compositions of soy foods and standardizing feeding protocol. Studies of specific soy phytochemicals (genistein, daidzein, etc.), oligosaccharides (stachyose and raffinose), and protein (β -conglycinin and glycinin) are rare in the literature. More studies in this area will also help elucidate their role in regulating gut microbiota and correlate specific soy components to specific changes in bacteria groups.

(4) Alternative End Points in Microbiota Functional Components. Previous studies of gut microbiota mostly focused on the population and composition of gut bacteria. The absence of “core” species in gut microbiota, together with the functional redundancy among bacteria, may contribute to the distinctive gut microbiota among individuals and inconsistent changes in bacterial composition observed in previous studies.^{40,41} The current understanding of the gut microbiota supported a set of “core” functional components at the gene level.⁴⁰ Therefore, future studies may consider alternative end points in functional components at the transcriptome or proteome level, instead of the genome level, which may help reveal more consensus changes upon soy or soy food supplementation.

(5) Population Studies. Experimental and clinical studies are usually limited by time and sample size. A population study may provide valuable information on the correlation between the consumption of soy food and its effect on the gut microbiota and its long-term health implications. Analysis of long-term consumption of diets rich in soy food, such as the Asian diet,¹⁵⁴ plus the understanding of the specific effect of soy components on gut bacteria may give insight into the shaping of the gut microbiota by soy/soy foods and potentially help explain the health disparity in culture and ethnic groups.

(6) In Utero and Transgenerational Effects. Consumption of the soy compound (genistein) during pregnancy was shown to alter the epigenome in offspring and have further health and disease implications.^{155,156} Previous studies have also shown that the gut microbiota plays a role in human development and

maturation of the immune system.^{157,158} It is not clear whether the changes in microbiota induced by soy consumption of the mother can lead to transgenerational effects or changes in initial inoculation of microbiota at birth. These effects may have a life-long health impact on the offspring. Therefore, experimental and longitudinal studies to assess changes in gut microbiota by soy consumption before and during pregnancy and the health outcome of the transgeneration offspring may provide important evidence for another dimension of soy's effects and overall health-promoting effect.

Soy is widely accepted to possess beneficial effects on human health. Recent studies have supported the importance of the gut microbiota and its health implication. The possible modulatory effects of soy/soy food on the gut microbiota provide an additional mechanism by which soy/soy foods can promote health. Future studies on the interaction between soy, gut microbiota, and the underlying mechanism of actions can provide valuable information to further establish soy as a health-promoting food to improve the health of the U.S. population.

AUTHOR INFORMATION

Corresponding Author

*(T.T.Y.W.) Phone: (301) 504-8459. E-mail: Tom.Wang@ars.usda.gov. Mail: 10300 Baltimore Avenue, USDA-ARS, BHNRC, Building 307C, Room 132, Beltsville, MD 20705, USA.

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