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Critical Review

Microbiota-Focused Dietary Approaches to Support Health: A Systematic Review

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A B S T R A C T

Diet affects the intestinal microbiota. Increasingly, research is linking the intestinal microbiota to various human health outcomes. Consumption of traditional prebiotics (inulin, fructo-oligosaccharides, and galacto-oligosaccharides) confers health benefits through substrate utilization by select intestinal microorganisms, namely *Bifidobacterium* and *Lactobacilli* spp. A similar but distinct concept focused on microorganisms to support human health is through direct consumption of certain live microorganisms recognized as probiotics, which classically include *Lactobacilli or Bifidobacterium* strains. With advances in sequencing technologies and culturing techniques, other novel functional intestinal microorganisms are being increasingly identified and studied to determine how they may underpin human health benefits. These novel microorganisms are targeted for enrichment within the autochthonous intestinal microbiota through dietary approaches and are also gaining interest as next-generation probiotics because of their purported beneficial properties. Thus, characterizing dietary approaches that nourish select microorganisms in situ is necessary to propel biotic-focused research forward. As such, we reviewed the literature to summarize findings on dietary approaches that nourish the human intestinal microbiota and benefit health to help fill the gap in knowledge on the connections between certain microorganisms, the metabolome, and host physiology. The overall objective of this systematic review was to summarize the impact of dietary interventions with the propensity to nourish certain intestinal bacteria, affect microbial metabolite concentrations, and support gastrointestinal, metabolic, and cognitive health in healthy adults. Findings from the 17 randomized controlled studies identified in this systematic review indicated that dietary interventions providing dietary fibers, phytonutrients, or unsaturated fatty acids differentially enriched *Akkermansia*, *Bacteroides*, *Clostridium*, *Eubacterium*, *Faecalibacterium*, *Roseburia*, and *Ruminococcus* species, with variable effects on microbial metabolites and subsequent associations with physiologic markers of gastrointestinal and metabolic health. These findings have implications for biotic-focused research on candidate prebiotic substrates as well as next-generation probiotics.

Keywords: dietary interventions, gut microbiota, prebiotics, probiotics, next-generation probiotics, fiber

Introduction

There is a profound interest in the connections between the intestinal microbiota and health. Diet is a crucial avenue by which one can impact the intestinal microbiota in ways that may affect health. Nondigestible dietary components, such as fiber, resistant starch, and prebiotics, are substrates for intestinal microorganisms [1], which results in microbial metabolite production [2] that may underpin beneficial physiologic responses to the diet [3]. Indeed, prebiotics are defined as substrates that are selectively used by host microorganisms and confer a health benefit [4]. A similar, yet distinct, approach focused on using microorganisms to support health is the dietary consumption of live microorganisms recognized as probiotics, which are live microorganisms that when consumed in adequate amounts confer health benefits upon the host [5]. Traditional probiotics such as *Bifidobacterium* spp and *Lactobacilli* spp have been studied for centuries and have a history of safe and effective use for various health outcomes [6]. Building on decades of research on the health benefits of prebiotics [7–12] and probiotics [13],

Abbreviations: BCFA, branched-chain fatty acid; CA, cholic acid; CDCA, chenodeoxycholic acid; CRP, C-reactive protein; DCA, deoxycholic acid; GLP, glucagon-like peptide; iAUC, incremental area under the curve; LBP, lipopolysaccharide-binding protein; LCA, lithocholic acid; LT, leukotriene; SCFA, short-chain fatty acids; TC, total cholesterol; TMAO, trimethylamine-*N*-oxide; TX, thromboxane.

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recent work has revealed that certain dietary patterns [14,15] and foods [16] affect the intestinal microbiota in ways that support health. These biotic-focused approaches, i.e., using dietary approaches to nourish the human intestinal microbiota to positively affect physiologic responses to the diet, are an area of intense research in the budding field of nutritional microbiology. Indeed, over the past decade, evidence has spurred discussions on the expansion of substrates recognized as prebiotics, which has not changed greatly since the term introduction in 1995, as well as considerations for next-generation probiotics, novel functional microorganisms (i.e., newly isolated) with health-promoting properties that may soon reach the level of evidence necessary to join the list of traditional probiotics.

Biotic-focused dietary research is fueled by advancements in molecular and computational approaches that allow scientists to identify and study the vast ecosystem of microorganisms residing in the human intestinal tract. Furthermore, culturomic approaches [17,18] allow scientists to isolate and study new microorganisms to determine their potential as next-generation probiotics [19]. As such, characterizing dietary approaches that nourish select microorganisms in situ is necessary to propel biotic-focused research forward, including research focused on candidate prebiotics and next-generation probiotics. To continue to expand this research area, we identified microorganisms of interest as potential next-generation probiotics, including *Akkermansia*, *Bacteroides*, *Clostridium*, *Eubacterium*, *Faecalibacterium*, *Roseburia*, and *Ruminococcus* species [6,20–23] and summarized the literature on dietary approaches that enriched these microorganisms within the human intestinal microbiota, which has relevance to discussions around the addition of candidate prebiotic substrates. Specifically, the objective of this systematic review was to identify randomized controlled clinical trials in healthy adults that studied the effects of well-defined dietary interventions on intestinal microorganisms, the metabolome, and gastrointestinal (GI), metabolic, and cognitive health outcomes.

Methods

We searched PubMed, Scopus, and the Cumulative Index to Nursing and Allied Health Literature in March 2024 for full-length articles written in English and published in peer-reviewed journals with no date restriction. Briefly, we divided search terms into the following 4 categories: *1*) microbiota (e.g., *Akkermansia, Bacteroides*, and *Clostridium* spp); *2*) metabolome [e.g., bile acids, short-chain fatty acids (SCFAs), and branched-chain fatty acids (BCFAs)]; *3*) metabolic, GI, and cognitive health outcomes (e.g., inflammation, blood glucose, laxation, flatulence, mood, and anxiety); and *4*) dietary interventions (e.g., Mediterranean diet and dietary fiber). The full search string for each database is included in Supplemental Table 1. Eligibility criteria are summarized in Table 1. Briefly, randomized controlled studies with well-described dietary intervention that significantly enriched the bacteria understudy, measured microbial metabolites, and benefited metabolic, GI, and/or cognitive health outcome(s) in healthy human adults without a diagnosed disease(s) (≥18 y of age)] were included. Studies with multiple treatment arms were included if ≥2 arm met the inclusion criteria. The full search strategy and details for the current review were registered in PROSPERO (CRD42023389894).

TABLE 1
Eligibility criteria for study inclusion in systematic review.

Inclusion criteria
1. Study design: full-length articles published in peer-reviewed journals; appropriate control (e.g., placebo), well-described dietary intervention(s), statistical methods included comparisons made between groups, statistically significant enrichment of bacterial abundance, inclusion of bacterial metabolites (e.g., bile acids, short-chain fatty acids), inclusion of health outcome(s) (e.g., metabolic, gastrointestinal, and/or cognitive), studies with ≥2 treatment arms
2. Participants: healthy human adults (≥18 y of age) without diagnosed disease(s)
3. Outcomes: reported significant enrichment of bacterial abundance, effects on bacterial metabolites, and health outcomes (i.e., metabolic, gastrointestinal, and/or cognitive)
4. Language: articles written in English
5. Year of publication: no date restrictions were applied
Exclusion criteria
1. Study design: reviews, cross-sectional studies, longitudinal studies, observational studies, in vitro studies, ex vivo studies, animal studies; no or inappropriate control, inadequately described dietary intervention(s), no between-group comparisons, no change or depletion of bacterial abundance, exclusion of bacterial metabolites, and exclusion of health outcome(s)
2. Participants: adults with a diagnosed disease(s), children, infants, or pregnant females
3. Outcomes: no significant enrichment of bacteria under study or no metabolic, gastrointestinal, and/or cognitive benefits
4. Language: not written in English
5. Full text: full text not received after contact

We followed the recommended PRISMA guidelines for article selection.

The title and abstract of nonduplicate articles were screened based on the abovementioned criteria. The remaining publications were reviewed in full by 2 authors (VKH, NMV), and reference lists of eligible articles were screened for additional publications not identified in the initial searches. A third author (HDH) resolved any discrepancies in study inclusion or exclusion. The 2 authors (VKH, NMV) extracted the data from studies meeting the selection criteria, including information on the study population (population characteristics, age, BMI in kg/m^2), diet intervention [type, duration, and dosage (if applicable)], and effects on the intestinal microbiota, bacterial metabolites, and health outcomes (metabolic, GI, or cognitive), compared with the control group.

To align with our objective to summarize research on biotic-enriching dietary approaches to support health, studies reporting dietary approaches that did not enrich the microorganisms under study or depleted the microorganisms were excluded from the final report.

Results and Discussion

Study selection and characteristics

Overall, this systematic review included 17 publications that reported significant enrichment of the candidate next-generation probiotics (*Akkermansia, Bacteroides, Clostridium, Eubacterium, Faecalibacterium, Roseburia, and Ruminococcus* species) (Figure 1), effects on microbial metabolites, and metabolic or GI health benefits (Figure 2). Of these publications, 2 reported enrichment of *Akkermansia*, 7 on *Bacteroides*, 3 on *Clostridium*, 1 on *Eubacterium*, 5 on *Faecalibacterium*, 5 on *Roseburia*, and 3 on

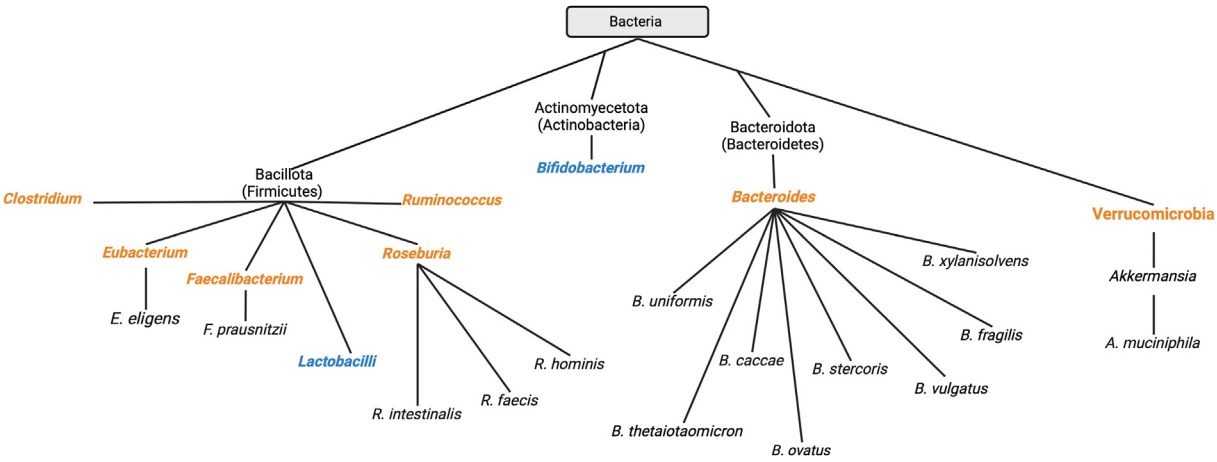

FIGURE 1. Characterization tree. This visual representation depicts the characterization between phylum, genus, and species of the studied next-generation probiotic candidates (in orange), as well as the classical probiotics, *Bifidobacterium* and *Lactobacilli* spp (in blue).

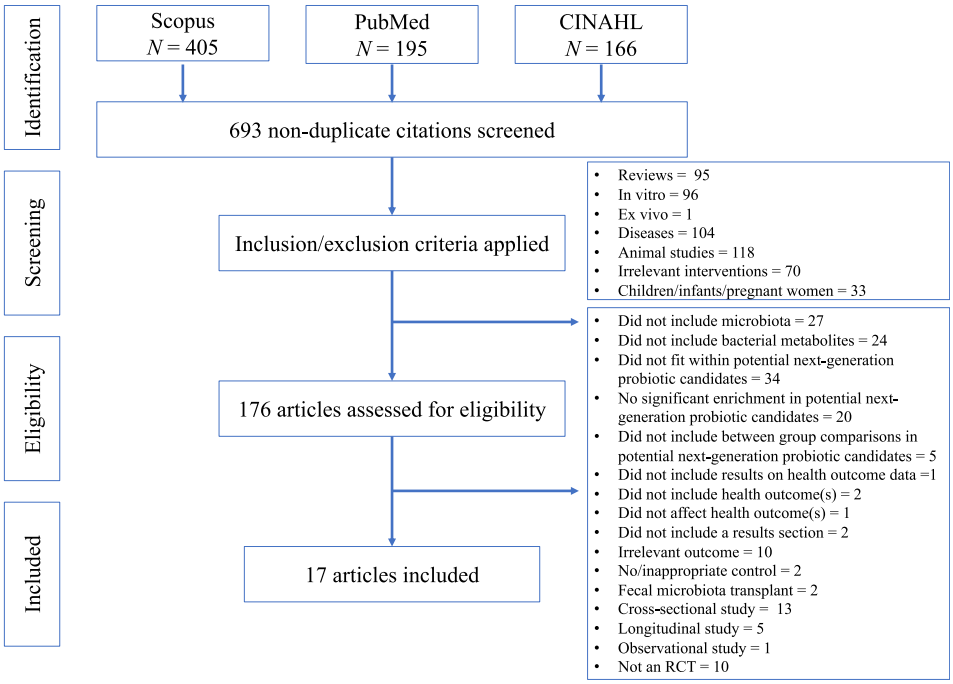

FIGURE 2. PRISMA flow diagram of article search and selection process. The literature search was conducted in March 2024 and included all full-length articles in English published in peer-reviewed journals with no date restrictions in PubMed, Scopus, and CINAHL. CINAHL, Cumulative Index to Nursing and Allied Health Literature.

Ruminococcus species. A summary of the biotic-focused dietary interventions that resulted in nonsignificant bacterial enrichment or depletion of these microbes can be found in Supplemental Tables 2 and 3, respectively. Additional details about the microbiota and metabolome methodology from the included trials are summarized in Supplemental Table 4.

The following sections summarize the effects of the well-defined nutritional interventions on *Akkermansia*, *Bacteroides*, *Clostridium*, *Eubacterium*, *Faecalibacterium*, *Roseburia*, and *Ruminococcus* species, bacterial metabolite concentrations, and GI, metabolic, and cognitive health outcomes.

Akkermansia species

Akkermansia spp are oval gram-negative, obligate anaerobes within the Verrucomicrobia phylum that colonize the intestinal mucosal layer in humans and rodents [24,25]. One of the main species, *Akkermansia muciniphila*, plays a key role in the human GI tract by maintaining intestinal integrity, improving gut barrier function, and colonizing the mucus layer [26]. *A muciniphila* signatures include metabolic regulation, host immune response, glucose metabolism, and improving inflammatory diseases and disorders [26]. *Akkermansia* sp. abundances have been reported to positively correlate with favorable health outcomes in mice and humans due to their production of metabolites such as acetate and propionate [25]. Of note, *Akkermansia* spp promote pancreatic β-cell growth through binding free fatty acid receptors 2 and 3 to secrete insulin and thereby contributing to blood glucose regulation [25,26]. This may explain the negative correlation between this species and the prevalence of type 2 diabetes mellitus in humans. Additionally, there is a negative

association between the abundance of *A muciniphila* and inflammatory bowel disease and obesity in humans. Similar outcomes have been observed in mice, including decreased inflammation and improved anticancer immunosurveillance [25,27,28].

The studies reporting dietary approaches that enrich *Akkermansia* sp. are detailed in Table 2 [29,30]. In the study by Vitale et al. [29], participants with overweight or obesity consumed a diet characterized by features of a traditional Mediterranean diet ($n = 16$) or an isocaloric habitual diet as the control, which included features of a typical western diet ($n = 13$), for 8 wk. The Mediterranean diet increased the relative abundance of *A muciniphila* compared with the control diet [29]. Fasting and postprandial concentrations of acetic and propionic acid did not change after the intervention in either group; however, postprandial plasma butyric acid concentrations significantly increased at the end of the intervention in the Mediterranean diet group, leading to a higher incremental AUC (iAUC) than that in the control group [29]. Postprandial plasma butyric acid iAUC at the end of the study inversely correlated with plasma insulin iAUC and directly correlated with oral glucose insulin sensitivity in the Mediterranean diet group, but not in the control [29]. Body weight, BMI, waist circumference, hip circumference, systolic blood pressure, and diastolic blood pressure values did not change throughout the study in either group [29]. Fasting plasma total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triglycerides concentrations did not differ between groups at baseline [29]. However, after 8 wk, LDL cholesterol was lower, triglycerides tended to be lower, and HDL cholesterol did not change in the Mediterranean diet group than those in the control [29]. Moreover, postprandial triglyceride response was not different between groups [29]. At the end of the study, plasma glucose and insulin responses remained lower than the baseline after the Mediterranean diet intervention and control, leading to an improved oral glucose insulin sensitivity index [29].

In the study by Xu et al. [30], participants with mild hypercholesterolemia not only consumed either oats containing 3 g of β-glucan and 56.8 mg polyphenol (80 g/d; $n = 94$) or control rice (80 g/d; $n = 93$) but also maintained their habitual diet for 45 d [30]. Oat consumption significantly increased the abundance of *A muciniphila* compared with the control [30]. Plasma acetic and propionic concentrations significantly increased following the oat intervention; however, similar trends were also seen in the control group [30]. There were no other significant effects found in either group among SCFA [30]. *A muciniphila* negatively correlated with HDL cholesterol concentrations and positively correlated with plasma acetic acid concentrations in the control group [30]. After the oat treatment, there were decreases in LDL cholesterol concentrations after days 30 (7.6%) and 45 (9.1%) [30]. In both groups, TC, and non–high-density lipoprotein cholesterol concentrations decreased after days 30 (5.7%) and 45 (8.7%); however, the reduction in total and non–HDL cholesterol concentrations was greater in those who consumed oats compared with that in those who consumed the control diet [30].

The dietary interventions used in these 2 studies differed—Vitale et al. [29] provided a Mediterranean diet and Xu et al. [30] provided oats. Consistencies found between both treatments include provision of diets that provide dietary fiber and a similar carbohydrate macronutrient profile [29,30]. Both studies reported a decrease in LDL cholesterol concentrations [29,30]. It is possible the decrease in LDL cholesterol concentrations

TABLE 2
Akkermansia species.

Reference	Study design (duration/washout duration)	Population characteristics/sample size, *N* (*n* intervention group)	Intervention (Dosage)	Comparator (dosage)	Microbial metabolite(s)	Health measures	Results
[29]	Randomized, controlled, parallel (8 wk/NA)	Adults with overweight or obesity, age 20–60 y, BMI 25–30 (male), BMI 30–35 (female)/$N = 29$ (16)	Mediterranean diet (NA)	Habitual diet—features of western diet (NA)	Plasma SCFA	Blood lipids, glycemic markers, anthropometric measurements	↑*Akkermansia* ↓Glucose response ↓Insulin response ↑Postprandial butyric acid iAUC ↓LDL cholesterol
[30]	Randomized, controlled, parallel, multicenter (45 d/NA)	Mildly hypercholesterolemic adults, age <50 or ≥50 y, BMI <24 or ≥24/$N = 187$ (94)	Oats (80 g/d) containing β-glucan+56.8 mg polyphenol	Rice (80 g/d)	Plasma SCFA	Blood lipids, anthropometric measurements	↑*Akkermansia* ↑Acetic acid ↑Propionic acid ↓TC ↓LDL cholesterol ↓Non–HDL cholesterol

Abbreviations: iAUC, incremental area under the curve; NA, not applicable; SCFA; short-chain fatty acid; TC, total cholesterol; TG, triglyceride.

observed could be attributed to the increase of *Akkermansia* spp. and their production of propionate, as propionate concentrations have previously been reported to be related to circulating cholesterol concentrations [31]. Both studies [29,30] reported correlations between microbial and physiological measures, including an inverse correlation between postprandial butyrate iAUC and insulin iAUC [29] and *A muciniphila* negatively correlating with HDL cholesterol concentrations [30].

Bacteroides species

Species within the *Bacteroides* genus are anaerobic, non–spore-forming, gram-negative rods in the Bacteroidota (previously Bacteroidetes) phylum and serve as one of the most prominent and dominant anaerobes that inhabit the human GI tract [32,33]. *Bacteroides* spp play multiple roles within the host creating commensal, mutualistic, and even some opportunistic pathogenic relationships. They possess the ability to break down glycans from both the host and diet depending on nutrient availability, through the utilization of mucin-type O-glycans [33,34]. This process not only generates mucus, which provides protection against pathogens, but also provides essential nutrients to other intestinal microbes. Moreover, *Bacteroides* spp have the ability to degrade polysaccharides, a process that plays a crucial role in maintaining the functionality and stability of gut microbiota. The resulting breakdown products, including monosaccharides and oligosaccharides, which are fermented by gut microbes to produce various metabolites, such as amino acids and SCFA, mainly acetate and propionate [34,35]. Specific to health, a decrease in the abundance of *Bacteroides* spp has been observed in patients and mice with obesity, and administration of certain *Bacteroides* spp. can improve glucose metabolism [24,36].

The studies reporting an enrichment of *Bacteroides* spp are detailed in Table 3 [37–43]. In the study by Tanihiro et al. [37], healthy females consumed yeast mannan (1.1 g/d; $n = 53$) or control maltose without yeast mannan ($n = 55$) for 8 wk. Yeast mannan intake selectively enriched the relative abundance of *Bacteroides thetainotamicron* and *Bacteroides ovatus* compared with the control [37]. There were no changes in *Bacteroides vulgatus, Bacteroides uniformis,* and *Bacteroides fragilis* observed between groups [37]. The changes in urinal equal concentrations were higher in the yeast mannan group than those in the control [37]. Supplementation of yeast mannan decreased fecal ammonia concentrations compared with the control [37]. Reductions were observed in fecal indole, skatole, and *p*-cresol concentrations in the yeast mannan group; however, there were no changes in fecal SCFA concentrations between groups [37]. The defecation frequency (days/week) was larger in the yeast mannan group than that in the control; however, there were no statistically significant differences in changes in defecation frequency between groups [37]. The changes found in fecal water content in the yeast mannan group were greater than that in the control [37]. All participants completed a constipation assessment scale to assess constipation symptoms [37]. Symptom scores in the yeast mannan group decreased, including inability to pass stool, less frequent bowel movements, and small volume of stool compared with the control group [37]. There were no differences in abdominal distention or, bloating, change in amount of gas passed rectally, rectal fullness or pressure, rectal pain with bowel movements, oozing liquid stool, and total constipation assessment scale score between both groups [37]. Consumption of yeast mannan alleviated some constipation symptoms, improved defecation frequency, and moistened feces [37]. There were no reported correlations between microbial and physiologic measures [37].

In the study by Chambers et al. [38], nondiabetic participants ($n = 12$) with overweight and obesity consumed 20 g/d of inulin-propionate ester, 20 g/d of high-fermentable inulin fiber (control), and 20 g/d of low-fermentable fiber cellulose (control) in a random order for 42 d [38]. Consumption of inulin-propionate ester resulted in a higher proportion of *Bacteroides caccae, B uniformis,* and *Bacteroides xylanisolvens* compared with cellulose control [38]. There were no differences in stool SCFA concentrations following the 3 supplemental periods; however, the molar percentage of fecal propionate was significantly higher following inulin-propionate ester consumption than that of the cellulose control [38]. No differences were observed within total or individual SCFA in fasting serum or postprandial blood among the 3 groups [38]. Both inulin-propionate ester and inulin control groups improved insulin sensitivity leading to a reduction in fasting insulin based on HOMA-IR and Matsuda index compared with the cellulose control group [38]. Consumption of inulin-propionate ester and inulin control improved adipose tissue insulin resistance [38]. However, the improvement in glucose homeostasis from the inulin-propionate ester and inulin control consumption was not associated with any changes in body weight, BMI, body fat percentage and weight, or fat free mass [38]. Serum immunoglobulin G concentrations increased and IL-8 concentrations decreased following inulin-propionate ester consumption compared with those after cellulose control consumption [38]. Other immunoglobulin and inflammatory markers including serum immunoglobulin A, immunoglobulin M, C-reactive protein (CRP), IL-6, IL-10, IL-12, and LPS-binding protein (LBP) concentrations did not change after all 3 supplementation periods [38]. There were no reported associations between microbial and physiologic measures; however, the authors did demonstrate that the addition of propionate to cultured human peripheral blood mononuclear cells reduced the secretion of IL-8 [38].

In the study by Wan et al. [39], healthy participants ($N = 217$) consumed 1 of the following 3 isocaloric diets that differed in fat content: low-fat diet (20% fat; $n = 73$), moderate-fat diet (30% fat; $n = 73$), or high-fat diet (40% fat; $n = 71$) for a duration of 6 mo [39]. Consumption of the high-fat diet increased the abundance of *Bacteroides* spp compared with that of the low-fat diet [39]. Total fecal SCFA concentrations decreased after the high-fat diet intervention compared with that after the low-fat and moderate-fat diets [39]. Fecal concentrations of indole, palmitic, stearic, arachidonic, and indoleacetic acids increased following high-fat diet consumption compared with those after the low-fat diet consumption [39]. Fecal *p*-cresol and indole concentrations decreased after the low-fat diet treatment; however, fecal 3-indolepropionic acid and butyric acid concentrations increased after low-fat consumption [39]. Fecal concentrations of butyric, valeric, and 3-indolepropionic acid reduced following consumption of the high-fat diet compared with those after the low-fat diet consumption [39]. The change in *Bacteroides* app positively correlated with changes in TC, LDL cholesterol, and non–HDL cholesterol concentrations [39]. In addition, *Bacteroides* spp positively correlated with changes in palmitic acid, indole, and *p*-cresol concentrations [39].

TABLE 3
Bacteroides species.

Reference	Study design (duration/washout duration)	Population characteristics/ sample size, *N* (*n* intervention group)	Intervention (dosage)	Comparator (dosage)	Microbial metabolite(s)	Health measures	Results
[37]	Randomized, double-blind, placebo-controlled (8 wk/NA)	Healthy females age, 30–49 y, BMI 20.5 ± 2.2 (intervention), BMI 21.0 ± 2.8 (control)/*N* =108 (49)	Yeast mannan (1.1 g/d)	Maltose (NA)	Fecal SCFA, fecal indole, fecal phenol, fecal ammonia, urinal equol	CAS, anthropometric measurements	↑*Bacteroides* ↓Isovalerate ↓p-cresol ↑Urinal equol ↓Indole ↓Skatole ↓Ammonia ↓Phenol + Indole ↓Constipation symptoms ↑Defection frequency ↑Fecal water content
[41]	Randomized, double-blind, placebo-controlled (12 wk/ NA)	Prediabetic male with overweight and obesity and postmenopausal females, age 45–70 y, BMI 28–40/*N* = 44 (21)	GOS (15 g/d)	Maltodextrin (~17 g/d)	Fecal SCFA, plasma SCFA, glycerol, FFA	Blood lipids, inflammatory markers, glycemic markers, hormones, anthropometric measurements	↑*Bacteroides*
[39]	Randomized, controlled-feeding, (6 mo/NA)	Healthy adults, age 18–35 y, BMI <28/*N* = 217 (lower-fat, 73; moderate-fat, 73; higher-fat, 71)	Lower-fat diet (20% fat, 66% carbohydrate) Moderate-fat diet (30% fat, 56% carbohydrate) Higher-fat diet (40% fat, 46% carbohydrate)	NA	Fecal SCFA, fecal LCFA, fecal phenol, fecal indole	Blood lipids, inflammatory markers, glycemic markers, anthropometric measurements	↑*Bacteroides* ↓Total SCFA ↑/↓Butyric acid ↑/↓Indole ↑/↓3-Indolepropionic ↑Palmitic acid ↑Stearic acid ↑Indoleacetic acid ↑Arachidonic acid ↓Valeric acid ↑/↓p-cresol ↑CRP ↑TXB2 ↓LTB4 ↓TC ↓LDL cholesterol ↓HDL cholesterol ↓Non–HDL cholesterol ↓BW ↓WC
[42]	Randomized, controlled-feeding, parallel (6 mo/NA)	Healthy adults, age 18–35 y, BMI <28/*N* = 120 (40/group)	Lower-fat diet (20% fat, 66% carbohydrate, 14% protein) Moderate-fat diet (30% fat, 56% carbohydrate, 14% protein)	NA	Fecal BA	Blood lipids, glycemic markers, liver function biomarkers, renal function biomarkers	↑*Bacteroides* ↑Total BAs ↑Unconjugated BAs ↑DCA ↑TDCA ↑12-keto-LCA ↑3β-DCA ↑TLCA

(*continued on next page*)

TABLE 3 (*continued*)

Reference	Study design (duration/washout duration)	Population characteristics/ sample size, *N* (*n* intervention group)	Intervention (dosage)	Comparator (dosage)	Microbial metabolite(s)	Health measures	Results
			Higher-fat diet (40% fat, 46% carbohydrate, 14% protein)				
[38]	Randomized, double-blind, placebo-controlled, crossover (42 d/28 d)	Nondiabetic adults with overweight and obesity, age 18–65 y, BMI 25–40/$N = 12$	Inulin-propionate ester (20 g/d)	High-fermentable fiber control (inulin 20 g/d) and low-fermentable fiber control (cellulose 20 g/d)	Fecal SCFA, fasting serum SCFA	Blood lipids, inflammatory markers glycemic markers, hormones, liver function markers, anthropometric measurements	↑*Bacteroides* ↓Fasting insulin ↓IL-8 ↑IgG
[40]	Randomized, open-label, crossover (10 d/ 10 d)	Healthy adults, regular breakfast/ lunch consumers ≥4 times/wk willing to consume meat+mushrooms, age 18–65 y, BMI 18.5–30/$N = 32$ (16)	*Agaricus bisporus* mushrooms (226 g/d)	Meat diet (28 g/d)	Fecal SCFA, fecal BCFA, breath hydrogen, breath methane	GI symptoms fecal biomarkers	↑*Bacteroides* ↑Average stool weight ↑Flatulence
[43]	Randomized, controlled (8 wk/NA)	Females with overweight or obesity at cardiometabolic risk, 20-55y, BMI ≥27 and <30, increased body fat (≥32%), increased waist circumference (≥80 cm)/$N = 40$ (25)	Brazil nuts (15 g/d)+ cashew nuts (30 g/d)	Free of nuts (−500 kcal/d)	Fecal SCFA	blood lipids, inflammatory markers, intestinal permeability, glycemic markers, anthropometric measurements	↑*Bacteroides* ↑Propionic acid ↓Acetic acid

Abbreviations: BA, bile acid; BW, body weight; DCA, deoxycholic acid; CRP, C-reactive protein; IgG, immunoglobulin G; LCA, lithocholic acid; LCFA, long-chain fatty acid; LT, leukotriene; NA, not applicable; SCFA, short-chain fatty acid; TC, total cholesterol; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TX, thromboxane; WC, waist circumference.

Moreover, the change in fecal arachidonic acid positively correlated with the changes in plasma thromboxane (TX) B_2 and CRP concentrations among all groups [39]. Plasma CRP concentrations increased during the consumption of the high-fat diet than that during the consumption of other 2 diets [39]. Plasma TXB_2 concentrations increased during high-fat diet consumption than that during low-fat diet consumption [39]. Plasma leukotriene (LT) B_4 concentrations decreased in the low-fat diet group compared with those in the other 2 groups; however, there were no changes other plasma cytokine markers including IL-1β, IL-6, IL-8, and TNF-α concentrations among all 3 interventions [39]. After 6 mo, all 3 diets observed decreases in body weight, although the reduction in weight was greater in the low-fat diet group than that in the high-fat diet group [39]. In addition, there was a greater reduction in waist circumference, TC, HDL cholesterol, non–HDL cholesterol, and LDL cholesterol concentrations in the low-fat diet than those in the high-fat diet [39]. However, TC/HDL cholesterol ratio did not differ for the duration of the study among all 3 diet interventions [39].

In the study by Hess et al. [40], healthy participants consumed *Agaricus bisporus* roasted mushrooms (226 g/d; $n = 16$) or meat diet as the control (28 g/d; $n = 16$) for 10 d [40]. There was an enrichment in *Bacteroides* spp after consumption of both diets, but significantly greater enrichment observed in *Bacteroides* spp after the mushroom diet compared with that after the control diet [40]. No differences were observed in fecal SCFA (acetate, propionate, and butyrate) or BCFA (isobutyrate and valerate) concentrations between groups [40]. However, isovalerate concentrations increased in the control compared with that in the mushroom diet [40]. On day 2, consumption of the mushroom diet increased GI symptoms including gas and flatulence compared with the control [40]. The most common GI symptoms included gas and flatulence between both groups [40]. On the last day of each condition, no differences were observed among GI symptoms between both groups [40]. Stool weights increased after consumption of the mushroom diet compared with that after the control; however, there were no differences observed in stool frequency, pH, or consistency between both groups [40]. In addition, there were no changes in breath hydrogen or methane concentrations between both groups [40]. There were no reported associations between microbial and physiologic measures [40].

In the study by Canfora et al. [41], participants who were prediabetic with overweight or obesity consumed 15 g/d of galacto-oligosaccharides ($n = 21$) or 15 g/d control maltodextrin ($n = 23$) along with their habitual diet for 12 wk. Consumption of galacto-oligosaccharides increased the abundance of *B stercoris et rel.* (0.83 ± 0.2-fold) compared with that of the control [41]. There were no effects observed on fecal or fasting plasma SCFA concentrations, including acetate, propionate, and butyrate in either group [41]. No differences were reported on gut-derived hormone concentrations, incretins, LBP, or other markers of inflammation [41]. BMI, body weight, body fat percentage, lean mass, and visceral tissue mass did not change from consumption of galacto-oligosaccharides compared with those of the control [41]. In addition, there were no effects observed on fasting plasma glucose, insulin, glycerol, free fatty acids, or triglyceride concentrations between groups [41]. No effects were reported on fasting plasma leptin, peptide YY, glucagon-like peptide (GLP)-1, IL-6, IL-8, TNF-α, and LBP concentrations from galacto-oligosaccharide supplementation compared with those of the control [41]. Insulin sensitivity did not change after galacto-oligosaccharide consumption compared with that after the control [41]. Likewise, there were no effects on HOMA-IR with either treatment [41]. Insulin-stimulated free fatty acid suppression did not change after galacto-oligosaccharide supplementation compared with that after the control [41]. Moreover, no changes were observed on insulin-stimulated respiratory quotient, fasting, and insulin-mediated fat and carbohydrate oxidation after either treatment [41]. There were no reported associations among microbial or physiologic measures [41].

In the study by Wan et al. [42], healthy participants ($N = 120$) consumed 1 of the following 3 isocaloric diets that differed in carbohydrate and fat content: low-fat diet (66% carbohydrate; 20% fat; $n = 40$), moderate-fat diet (56% carbohydrate; 30% fat; $n = 40$), or high-fat diet (46% carbohydrate; 40% fat; $n = 40$) for 6 mo. The abundance of *Bacteroides* spp consistently significantly increased after the high-fat diet compared with that after both the moderate and low-fat diets [42]. The high-fat diet resulted in an increase in total bile acid concentrations compared with the moderate and low-fat diets [42]. Unconjugated bile acid concentrations increased in the high-fat diet compared with those in the low-fat diet [42]. Fecal deoxycholic acid (DCA) and 12-keto lithocholic acid (LCA) bile acid concentrations increased in the high-fat diet compared to the low-fat diet [42]. Fecal DCA and taurodeoxycholic acid bile acid concentrations also increased after the high-fat diet compared to the moderate-fat diet [42]. After 6 mo, all 3 treatments led to a decrease in body weight, although the reduction in weight was greater in the low-fat diet group compared to the high-fat diet group [42]. There was a greater reduction in TC, HDL cholesterol, non–HDL cholesterol, LDL cholesterol concentrations, and waist circumference in the low-fat diet group than that in the high-fat diet group [42]. However, the TC to HDL cholesterol ratio among all 3 diet interventions did not differ for the duration of the study [42]. Plasma CRP concentrations increased during the high-fat diet treatment compared to the other 2 treatment groups [42]. Plasma concentrations of TXB2 increased after the high-fat diet compared with the low-fat diet [42]. Plasma LTB4 concentrations decreased in the low-fat diet compared with the other 2 groups [42]. There were no changes to plasma IL-1B, IL-6, IL-8, and TNF-α concentrations among all 3 dietary interventions [42]. The changes in total, unconjugated, and 12-keto-LCA bile acid concentrations, as well as the change in fecal DCA concentrations, positively correlated with the change in *Bacteroides* sp relative abundance. Total and unconjugated bile acid changes correlated negatively with changes in TC and HDL cholesterol concentrations, whereas the changes in fecal DCA and 12-keto-LCA bile acid concentrations correlated negatively only with changes in TC concentrations [42]. Moreover, the changes in fecal arachidonic acid concentrations positively correlated with the changes in plasma TXB_2 and CRP concentrations [42].

In the study by Silveira et al. [43], female participants ($N = 40$) with overweight and obesity at cardiometabolic risk were assigned to energy-restricted groups: control group free of nuts (−500 kcal/d) or Brazil nut group (30 g of cashew nuts and 15 g of Brazil nuts per day) for 8 wk. In the 25 females who completed the study, the Brazil nut group increased the relative abundance of *Bacteroides* sp compared with the control group [43]. The Brazil nut group also experienced significant increases in fecal

propionic acid concentrations compared with those in baseline; however, there were no differences observed between groups [43]. Consumption of Brazil nuts significantly decreased acetic acid concentrations compared with the control diet consumption [43]. Butyric acid and fecal pH did not significantly change from baseline or between treatments [43]. Both groups, compared with baseline, had reductions in weight loss, waist circumference, hip circumference, BMI, and body fat, but there were no differences between groups [43]. Regarding inflammatory markers, there were no changes observed in plasma concentrations of CRP, TNF, IL-6, IL-8, IL-10, and IL-17A [43]. Lactulose-to-mannitol ratio and mannitol excretion did not differ between treatments; however, the control group had higher lactulose excretion than the Brazil nuts group [43]. Lactulose-to-mannitol ratio positively correlated with reductions in percentage of body fat and IL-8 concentrations [43]. Reductions in lactulose excretion positively correlated with reductions in percentage of body fat and BMI [43]. Changes in intestinal permeability correlated to a greater reduction in body fat percentage and IL-8 concentrations [43]. There were no associations among *Bacteroides* sp. abundance, bacterial metabolites, and physiological measures [43].

The dietary interventions used in the aforementioned 7 studies were similar in their provision of sources of dietary fiber as the intervention or as part of a meal [37–43]. Both studies conducted by Wan et al. [39,42] provided the same macronutrient profiles including carbohydrates, protein, and fat. Silveira et al. [43] used Brazil and cashew nuts as dietary interventions in their study. Tanihiro et al. [37], Chambers et al. [38], Hess et al. [40], and Canfora et al. [41], all used soluble fiber as their intervention of choice. All studies that analyzed fecal SCFA reported no effects of the interventions on fecal SCFA concentrations [38,41,43]. Chambers et al. [38], Canfora et al. [41], Wan et al. [42], and Silveira et al. [43] did not observe changes to IL-6 concentrations. Wan et al. [39,42], Canfora et al. [41], and Silveira et al. [43] reported no effects on IL-8 or TNF-α concentrations. Chambers et al. [38] and Silveira et al. [43] did not observe changes to CRP or IL-10 concentrations. In addition, Chambers et al. [38] and Canfora et al. [41] reported no effects to LBP concentrations. Both studies conducted by Wan et al. [39, 42] observed decreases in TC, HDL cholesterol, non–HDL cholesterol, LDL cholesterol concentrations, and other improvements in metabolic outcomes within the low-fat diet group. Even though *Bacteroides spp*. are known for producing acetate and propionate, none of the studies included observed effects on fecal SCFA concentrations. Two studies reported associations between microbial and physiologic outcomes: in 2019, Wan et al. [39] reported that the change of *Bacteroides* sp. relative abundance correlated positively with changes in TC, LDL cholesterol, and non–HDL cholesterol concentrations, and in 2020 [42], they reported that changes in total and unconjugated bile acid concentrations correlated negatively with changes in TC and HDL cholesterol concentrations, whereas the changes in fecal DCA and 12-keto-LCA bile acid concentrations correlated negatively only with changes in TC concentrations [42].

Clostridium species

Clostridium is a diverse genus. Some of the more beneficial effects in the body include regulating and maintaining intestinal functions, energizing intestinal cells, strengthening the intestinal barrier, and interacting with the immune system [44–46]. These microorganisms are among the earliest colonizers of the intestinal tract and produce metabolites such as butyrate and indolepropionic acid that regulate and maintain intestinal functions [44, 45]. They are anaerobic, gram-positive rods within the Bacillota (previously Firmicutes) phylum. Furthermore, they are chemo-organotrophic, meaning they can ferment a diverse range of nutrients, including carbohydrates, proteins, organic acids, fiber, and other organic compounds [44,45]. Consequently, *Clostridum* spp. produce gases, solvents, and SCFA such as butyrate and acetate, which may have positive effects on the body [44–47]. Interestingly, oral administration of *Clostridium butyricum* can alleviate obesity in Sprague-Dawley rats, including improvements in adiposity, energy storage, and metabolism [48].

Results of the studies summarized in this review reporting an enrichment of *Clostridium* are reported in Table 4 [42,49,50]. In the study by Holscher et al. [49], healthy participants ($N = 18$) consumed isocaloric diets containing 0 g (control) or 42 g/d of walnuts for two 3-wk periods with a 1-wk washout between conditions. The walnut intervention resulted in a higher relative abundance of *Clostridium* spp. compared with the control [49]. Fecal DCA and LCA concentrations were 25% and 45% lower, respectively, with walnut consumption compared with those in the control diet consumption [49]. LDL cholesterol concentrations and noncholesterol sterol campesterol concentrations were 7% and 6% lower, respectively, following walnut consumption compared with those after the control diet consumption [49]. The relative abundance of fecal *Clostridium* spp was not associated with TC or LDL cholesterol concentrations at the end of the walnut consumption period [49].

In the study by Wan et al. [42], healthy participants ($N = 120$) consumed 1 of the following 2 isocaloric diets that differed in carbohydrate and fat content: low-fat diet (20% fat; 66% carbohydrate; 14% protein; $n = 40$), moderate-fat diet (30% fat; 56% carbohydrate; 14% protein; $n = 40$), or high-fat diet (40% fat; 46% carbohydrate; 14% protein; $n = 40$) for 6 mo [42]. The abundance of *Clostridium* sp. consistently significantly increased after the high-fat diet compared with that after both the moderate and low-fat diets [42]. The high-fat diet resulted in an increase in total bile acid concentrations compared with the moderate and low-fat diets [42]. Unconjugated bile acid concentrations increased in the high-fat diet compared with the low-fat diet [42]. Fecal DCA and 12-keto-LCA bile acid concentrations increased in the high-fat diet compared with those after the low-fat diet [42]. Fecal DCA and taurodeoxycholic acid bile acid concentrations also increased after the high-fat diet compared with those after the moderate-fat diet [42]. After 6 mo, all 3 treatments led to a decrease in body weight, although the reduction in weight was greater in the low-fat diet group compared with that in the high-fat diet group [42]. There was a greater reduction in TC, HDL cholesterol, non–HDL cholesterol, LDL cholesterol concentrations, and waist circumference in the low-fat diet group compared with those in the high-fat diet group [42]. However, the TC-to HDL cholesterol ratio among all 3 diet interventions did not differ for the duration of the study [42]. Plasma CRP concentrations increased during the high-fat diet treatment compared with the other 2 treatment groups [42]. Plasma concentrations of TXB_2 increased after the high-fat diet compared with that after the low-fat diet [42]. Plasma LTB_4 concentrations decreased in the low-fat diet compared with that

TABLE 4
Clostridium species.

Reference	Study design (duration/ washout duration)	Population characteristics/ sample size, *N* (*n* intervention group)	Intervention (dosage)	Comparator (dosage)	Microbial metabolite(s)	Health measures	Results
[49]	Randomized, controlled-feeding, crossover (3 wk/1 wk)	Healthy adults, age 35–67.8 y, BMI 20.2–34.9/*N* = 18	Isocaloric diet+walnuts (42 g)	Isocaloric diet (NA)	Fecal BA	Blood lipids, inflammatory markers, glycemic markers, noncholesterol sterol, anthropometric measurements	↑*Clostridium* ↓DCA ↓LCA ↓LDL cholesterol ↓Noncholesterol sterol campesterol
[42]	Randomized, controlled-feeding, parallel (6 mo/NA)	Healthy young adults, age 18–35 y, BMI <28/*N* = 217 (73; lower-fat, 73; moderate-fat, 71; higher-fat)	Lower-fat diet (20% fat, 66% carbohydrate, 14% protein) Moderate-fat diet (30% fat, 56% carbohydrate, 14% protein) Higher-fat diet (40% fat, 46% carbohydrate, 14% protein)	NA	Fecal BA	Blood lipids, glycemic markers, liver function biomarkers, renal function biomarkers	↑*Clostridium* ↑Total BAs ↑Unconjugated BAs ↑DCA ↑TDCA ↑12-keto-LCA ↑3β-DCA ↑TLCA
[50]	Randomized, double-blind, placebo-controlled, crossover (4 wk/6 wk)	Overweight and obese adults, age 35–65 y, BMI 28–35/*N* = 22	FruitFlow (2 × 150 mg)	Maltodextrin (NA)	Fecal SCFA, plasma SCFA, fecal BA, plasma BA, organic acids	Inflammatory markers, anthropometric measurements	↑*Clostridium* ↓Urine TMAO ↓Plasma LPS

Abbreviations: BA, bile acid; DCA, deoxycholic acid; LCA, lithocholic acid; LPS, lipopolysaccharide; NA, not applicable; SCFA; short-chain fatty acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TMAO, trimethylamine-*N*-oxide.

in the other 2 groups [42]. There were no changes to plasma IL-1B, IL-6, IL-8, and TNF-α concentrations among all 3 dietary interventions [42]. The change in abundance of *Clostridium* spp with bile acid concentrations was not reported. However, total and unconjugated bile acid changes correlated negatively with changes in TC and HDL cholesterol concentrations, whereas the changes in fecal DCA and 12-keto-LCA bile acid concentrations correlated negatively only with changes in TC concentrations [42]. Moreover, the changes in fecal arachidonic acid concentrations positively correlated with the changes in plasma TXB_2 and CRP concentrations [42].

In the study by Rehman et al. [50], participants ($N = 22$) with overweight and obesity consumed FruitFlow, a water-soluble tomato extract (300 mg/d), or control maltodextrin for 4 wk with a 6-wk washout between conditions. Consumption of FruitFlow increased *Clostridium carnis* compared with the control diet consumption [50]. There were no between-group differences in fecal SCFA; however, valerate increased from baseline to end of the intervention in the control group [50]. There were no differences between-group differences in plasma bile acids; however, there were several changes within groups [50]. Chenodeoxycholic acid (CDCA), glycocholic acid, and glycodeoxycholic acid concentrations increased in the FruitFlow group [50]. No significant between-group differences were observed in fecal bile acids; however, fecal cholic acid (CA) increased from baseline to end of intervention in the FruitFlow group, but not in the control [50]. The FruitFlow treatment decreased fasting plasma and urine trimethylamine-*N*-oxide (TMAO) concentrations from baseline to the end of intervention; however, these changes were statistically significant only for urine TMAO concentrations when comparing between the groups [50]. No significant between-group differences were observed in plasma LPS concentrations; however, there was a significant within-group change with reduced plasma LPS concentrations at the end of the intervention when compared with baseline in the FruitFlow group, but not in the control [50]. Moreover, there were no significant between or within-group GI symptoms [50]. There were no reported correlations between *Clostridium* sp. or metabolites and physiologic measures [50].

The dietary treatments used in the aforementioned 3 studies differed. Holscher et al. [49] provided a walnut intervention, Wan et al. [42] provided 3 diets that differed in fat and carbohydrate contents, and Rehman et al. [50] provided FruitFlow, a water-soluble tomato extract intervention. Both the moderate-fat diet and walnut treatment provided dietary fiber and similar macronutrient profiles including fat, carbohydrates, and protein [42,49]. However, no consistencies were found between the walnut intervention and low-fat or high-fat diets [42,49]. In addition, no consistencies were found between the FruitFlow and walnut interventions or FruitFlow intervention or high-fat, moderate-fat, or low-fat diets [42,49,50]. Holscher et al. [49] and Wan et al. [42] reported reductions in LDL cholesterol concentrations. It is possible that the ability of *Clostridium* spp. to produce SCFA [44,45] could have played a role in the observed decrease in LDL concentrations. Among these 3 studies, the association between *Clostridium* and total and LDL cholesterol concentrations was assessed in only 1 study (no significant

association) [49]; there were no other reported associations between *Clostridium* spp and physiologic outcomes. Specific to microbial metabolites, 1 study reported that the changes in fecal DCA and 12-keto-LCA bile acid concentrations correlated negatively with changes in TC concentrations [42].

Eubacterium species

Eubacterium spp can be difficult to define due to their extensive phylogenetic diversity. Generally, these microorganisms are recognized as gram-positive, non–spore-forming rods. They are also chemo-organotrophic organisms and belong to the Bacillota (previously Firmicutes) phylum [51–53]. Because *Eubacterium* spp are major butyrate producers, they play a role in many physiologic processes such as energy, suppression of inflammation, SCFA production, cholesterol metabolism, bile acid metabolism, and metabolic transformations [51–56]. They are shown to be correlated with positive cardiovascular, hepatic, and metabolic health outcomes as shifts in microbial diversity and dysbiosis have been seen in patients with diseases within these areas [52,55,56].

Findings from the study reporting an enrichment of *Eubacterium* spp are outlined in Table 5 [57]. In the study by Zhang et al. [57], participants with prediabetes ($n = 26$) or who were metabolically healthy ($n = 10$) consumed 125 g of polyphenol-dense red raspberries alone as the control or polyphenol-dense red raspberries+8 g/d of fructo-oligosaccharides for two 4-wk periods with a 4-wk washout in between conditions. Consumption of polyphenol-dense red raspberries after 4 wk significantly increased the abundance of *Eubacterium eligens* (2-fold) in the prediabetes group compared with that in the control [57]. The supplementation of polyphenol-dense red raspberries+fructo-oligosaccharides increased several microbial-derived fatty acids compared with the control [57]. Whole-body fat percentage, whole-body fat mass, and trunk fat mass increased after polyphenol dense-red raspberries+fructo-oligosaccharide supplementation from baseline in the control group; however, there were no changes in body weight or composition variables within the prediabetes group after supplementation of polyphenol-dense red raspberries alone [57]. In the prediabetes group, supplementation of polyphenol-dense red raspberries decreased hepatic insulin resistance by ~30% compared with the control [57]. Supplementation of polyphenol-dense red raspberries+fructo-oligosaccharides in the prediabetes group increased the disposition index and insulin secretion rate leading to improved β-cell function compared with the control [57]. Neither treatment had an impact on glycemic status in the control group [57]. In the prediabetes group, supplementation of polyphenol-dense red raspberries decreased TC and LDL cholesterol concentrations compared with the control [57]. TC was lower after 4 wk of supplementation of polyphenol-dense red raspberries compared with 4 wk of polyphenol-dense red raspberries+fructo-oligosaccharide supplementation [57]. The LDL cholesterol/HDL cholesterol ratio decreased postsupplementation of polyphenol-dense red raspberries compared with baseline and postsupplementation of polyphenol-dense red raspberries+fructo-oligosaccharide supplementation [57]. Both polyphenol-dense red raspberries alone and polyphenol-dense red raspberries+fructo-oligosaccharides had no effect on lipids, blood pressure, or atherogenic risk markers in the control group [57]. Plasma IL-10 concentrations slightly increased from baseline after polyphenol-dense red raspberries+fructo-oligosaccharide supplementation compared with polyphenol-dense red raspberries supplementation alone, which was not influenced [57]. Changes in the relative abundance of *E eligens* correlated negatively with changes in TC, LDL cholesterol, and LDL cholesterol/HDL cholesterol ratio concentrations and tended to be associated with changes in plasma IL-10 concentrations [57].

Although there was only 1 study that aligned with our inclusion criteria, other studies reported similar effects regarding *Eubacterium* spp. For example, Ghosh et al. [58] conducted a longitudinal study and provided a Mediterranean diet pattern to elderly subjects across 5 European countries and reported a

TABLE 5
Eubacterium species.

Reference	Study design (duration/ washout duration)	Population characteristics/ sample size, *N* (*n* intervention group)	Intervention (dosage)	Comparator (dosage)	Microbial metabolite(s)	Health measures	Results
[57]	Randomized, controlled, crossover (4 wk/4 wk)	Adults at cardiometabolic risk with prediabetes and insulin resistance (fasting glucose 5.7 ± 0.1 mmol/L; HOMA-IR 3.3 ± 0.3), age 35 ± 2 y, or metabolically healthy adults (fasting glucose 5.1 ± 0.2 mmol/L; HOMA-IR 1.1 ± 0.1), age 31 ± 3 y/ *N* = 36 (26)	RRB alone (125 g/ d) or RRB (125 g/ d)+FOS (8 g/d)	NA	Fatty acids	Blood lipids, inflammatory markers, glycemic markers, anthropometric measurements	↑*Eubacterium* ↑Fatty acids ↓TC ↓LDL cholesterol ↓LDL cholesterol/ HDL cholesterol ↑IL-10 ↑ISR ↑DI ↓Hepatic-IR

Abbreviations: DI, disposition index; FOS, fructo-oligosaccharide; GOS, galacto-oligosaccharide; IR, insulin resistance; ISR, insulin secretion rate; NA, not applicable; RRB, (poly)phenol-dense red raspberries; SCFA; short-chain fatty acid; TC, total cholesterol.

significant enrichment in *E eligens*, increased metabolite production, and improved metabolic measures.

Faecalibacterium species

Faecalibacterium prausnitzii serves as one of the most prevalent bacteria in the intestinal microbiota of healthy adults, making ≤5% to 15% of the total bacterial population [59,60,61]. Despite its prevalence, there is limited information on the species outside of a few characteristics. *Faecalibacterium* spp belong to the Bacillota (previously Firmicutes) phylum and are anaerobic, hard to cultivate, and one of the most abundant butyrate producers [59,60,62,63]. Because of their ability to synthesize butyrate along with other metabolites, they can provide energy to colonocytes and modulate the immune system [61]. Moreover, *Faecalibacterium* spp have the ability to stimulate the production of anti-inflammatory cytokine IL-10, inhibit transcription nuclear factor-κB, and inhibit the production of proinflammatory cytokines [59,60,61,64]. Moreover, there have been reported links between *Faecalibacterium* spp. and superior gut barrier function, improved glucose tolerance, and reduced gut inflammation [60,61].

Results of studies reporting dietary approaches that enriched *Faecalibacterium* spp are reported in Table 6 [42,49,65–67]. In the study by Thompson et al. [65], participants with overweight or obesity consumed isocaloric meals with fresh Hass avocado (n = 55; 175 g/d; men or 140 g/d; women) or without avocado as the control (n = 54) once daily for 12 wk. Avocado consumption enriched the relative abundance of *Faecalibacterium* spp compared with the control [65]. Fecal acetate concentrations were 18% higher after avocado consumption compared with those after the control diet [65]. Following the avocado treatment, stearic and palmitic acid concentrations increased by 70% and 98%, respectively, compared with those after the control diet [65]. In the avocado group, CA and CDCA bile acid concentrations were 91% and 57% lower, respectively, compared with those after the control diet [65]. Fecal CA, LCA, and total bile acid concentrations tended to be lower after avocado consumption compared with those after the control diet [65]. Body weight, BMI, and visceral adiposity decreased in both groups; however, body weight did not differ between groups after 12 wk [65]. Correlational analyses among *Faecalibacterium* spp, fecal metabolites, and metabolic outcomes were undertaken, revealing no associations among the variables [65].

In the study by West et al. [66], healthy active participants consumed 20 g of butyrylated high-amylose maize starch (n = 17) daily or 20 g of control (low-amylose maize starch; n = 23) daily for 28 d. High-amylose maize starch enriched the relative abundance of F *prausnitzii* (5.1-fold) from day 0 to day 28 compared with the control (low-amylose maize starch) [66]. There were significant increases in fecal free, bound, and total butyrate from day 0 to day 28 after high-amylose maize starch consumption compared with those after the control (low-amylose maize starch) [66]. In addition, fecal propionate concentrations increased by 41% from day 0 to day 28 after high-amylose maize starch consumption compared with those after the control (low-amylose maize starch) [66]. The ratio of fecal acetate-to-propionate decreased by 30% after consumption of high-amylose maize starch compared with that after the control (low-amylose maize starch) over the duration of the study [66]. No differences were observed in total fecal SCFA concentrations from presupplementation to postsupplementation between groups [66]. Plasma IL-1 receptor antagonist concentrations increased (1.9-fold) from day 0 to day 14 in the high-amylose maize starch group with those after the control (low-amylose maize starch) group; however, from day 0 to day 28, there was only a slight difference between groups [66]. Supplementation of high-amylose maize starch increased plasma TNF-α (2.5-fold) and IL-10 (1.6-fold) concentrations compared with the control (low-amylose maize starch) from day 0 to day 28 [66]. There were no observed effects with other plasma cytokine markers including IL-6, IL-8, interferon γ, or granulocyte macrophage colony-stimulating factor concentrations in either group [66]. The consumption of high-amylose maize starch was not associated with any changes in GI discomfort symptoms measured by the GI quality of life questionnaire [66]. Covariate analysis did not reveal any trends between changes in *F prausnitzii* and changes in SCFA. There were no other reported correlations between microbial and physiologic measures [66].

In the study by Wan et al. [39], healthy participants (N = 217) consumed 1 of the following 3 isocaloric diets that differed in fat content: low-fat diet (20% fat; n = 73), moderate-fat diet (30% fat; n = 73), or high-fat diet (40% fat; n = 71) for a duration of 6 mo. Consumption of the low-fat diet significantly increased the relative abundance of *Faecalibacterium* spp. Total fecal SCFA concentrations decreased after the high-fat diet intervention compared with those after the low and moderate-fat diet groups [39]. Fecal concentrations of indole, palmitic, stearic, arachidonic, and indoleacetic acid increased following high-fat diet consumption compared with those after the low-fat diet [39]. Fecal *p*-cresol and indole concentrations decreased after the low-fat diet treatment; however, fecal 3-indolepropionic acid and butyric acid concentrations increased after low-fat consumption [39]. Fecal concentrations of butyric, valeric, and 3-indolepropionic acids reduced following consumption of the high-fat diet compared with those after the low-fat diet [39]. The change in *Faecalibacterium* spp positively correlated with the change of butyric acid in the low-fat diet group [39]. Moreover, the change in fecal arachidonic acid positively correlated with the changes in plasma TXB_2 and CRP concentrations among all groups [39]. Plasma CRP concentrations increased in the high-fat diet compared with those in the other 2 groups [39]. Plasma TXB_2 concentrations increased during high-fat diet consumption compared with those after the low-fat diet [39]. Plasma LTB_4 concentrations decreased in the low-fat diet group compared with those in the other 2 groups; however, there were no changes other plasma cytokine markers including IL-1B, IL-6, IL-8, and TNF-α among all 3 interventions [39]. After 6 mo, all 3 diets observed decreases in body weight, although the reduction in weight was greater in the low-fat diet group than that in the high-fat diet group [39]. In addition, there was a greater reduction in waist circumference, TC, HDL cholesterol, non–HDL cholesterol, and LDL cholesterol in the low-fat diet than those in the high-fat diet [39]. However, TC/HDL cholesterol ratio among all 3 diet interventions did not differ for the duration of the study [39]. Although there was a positive correlation between the change in *Faecalibacterium* sp. relative abundance and the change in fecal butyrate concentrations, there were no reported correlations between microbial and physiologic measures [39].

In the study by Meslier et al. [67], sedentary participants with overweight and obesity and a low intake of fruit and vegetables

TABLE 6
Faecalibacterium species.

Reference	Study design (duration/ washout duration)	Population characteristics/ sample size, *N* (*n* intervention group)	Intervention (dosage)	Comparator (dosage)	Microbial metabolite(s)	Health measures	Results
[65]	Randomized, Controlled, Investigator-Blinded, Parallel (12 wk/NA)	Adults with overweight and obesity, age 25-45y, BMI ≥25.0/ *N* = 109 (55)	Fresh Hass avocado (175 g/ d; male 140 g/d; female)	Isocaloric control meal without fresh Hass avocado (NA)	Fecal SCFA, Fecal BCFA, Fecal BA, Fecal FA	Inflammatory markers, Glycemic markers, Anthropometric measurements	↑*Faecalibacterium* ↑Acetate ↑Stearic acid ↑Palmitic acid
[66]	Randomized, controlled, double-blind, parallel (28 d/ NA)	Healthy active adults, (male) age, 37.9 ± 7.8 y (female) age, 36.9 ± 9.5 y /*N* = 51 (23 male; 18 female)	HAMSB (40 g/d)	LAMS (40 g/d)	Fecal SCFA, fecal ammonia	Inflammatory markers, fecal biomarkers, GI symptoms	↑*Faecalibacterium* ↑Butyrate ↑Propionate ↑TNF-α ↑IL-10
[67]	Randomized, controlled two-armed, parallel (8 wk/NA)	Adults with overweight and obesity, age ≥20 to ≤65 y, BMI ≥24/*N* = 82 (43)	Mediterranean diet (NA)	Habitual diet (NA)	Fecal SCFA, fecal BCFA, fecal BA, urolithins	Blood lipids, inflammatory markers, glycemic markers, hormones, chemicals, anthropometric measurements	↑*Faecalibacterium* ↓TC ↓HDL cholesterol ↓Total BAs ↓DCA ↓LCA ↓CDCA ↓Valerate ↓Isovalerate ↓Isobutyrate ↓2-methylbutyrate ↑Urolithin glucuronides
[42]	Randomized, controlled-feeding (6 mo/ NA)	Healthy adults, age 18–35 y, BMI <28/*N* = 217 (lower-fat, 73; moderate-fat, 73; higher-fat, 71)	Lower-fat diet (20% fat, 66% carbohydrate) Moderate-fat diet (30% fat, 56% carbohydrate) Higher-fat diet (40% fat, 46% carbohydrate)	NA	Fecal SCFA, fecal LCFA, fecal phenol, fecal indole	Blood lipids, inflammatory markers, glycemic markers, anthropometric measurements	↑*Faecalibacterium* ↓Total SCFA ↑/↓Butyric acid ↑/↓Indole ↑/↓3-Indolepropionic ↑Palmitic acid ↑Stearic acid ↑Indoleacetic acid ↑Arachidonic acid ↓Valeric acid ↑/↓p-cresol ↑CRP ↑TXB2 ↓LTB4 ↓TC ↓LDL cholesterol ↓HDL cholesterol ↓Non–HDL cholesterol ↓BW ↓WC
[49]	Randomized, controlled-feeding, crossover (3 wk/ 1 wk)	Healthy adults, age 35–67.8 y, BMI 20.2–34.9/ *N* = 18	Isocaloric diet+walnuts (42 g/d)	Isocaloric diet (NA)	Fecal BA	Blood lipids, inflammatory markers, glycemic markers, noncholesterol sterol, anthropometric measurements	↑*Faecalibacterium* ↓DCA ↓LCA ↓LDL cholesterol ↓Noncholesterol sterol campesterol

Abbreviations: BA, bile acid; BW, body weight; CDCA, chenodeoxycholic acid; CRP, C-reactive protein; DCA, deoxycholic acid; LT, leukotriene; LCA, lithocholic acid; LCFA, long-chain fatty acid; NA, not applicable; SCFA, short-chain fatty acid; TC, total cholesterol; TX, thromboxane; WC, waist circumference.

consumed the Mediterranean diet isocaloric and were compared with those who consumed their habitual diet ($n = 43$) or maintained their habitual diet (control; $n = 39$) for 8 wk [67]. Consumption of the Mediterranean diet increased levels of *Faecalibacterium* spp after 4 and 8 wk compared with the control [67]. In addition, consumption of the Mediterranean diet decreased fecal bile acid concentrations compared with the control [67]. Specifically, consumption of the Mediterranean diet reduced fecal DCA and LCA concentrations after 4 and 8 wk [67]. After 8 wk, there was a reduction in CDCA concentrations when comparing the Mediterranean diet with the control [67]. Urolithin urinary concentrations increased after consumption of the Mediterranean diet compared with those after the control [67]. No changes in fecal SCFA concentrations including acetate, propionate, and butyrate were observed following the Mediterranean diet [67]. However, fecal BCFA including valerate, isovalerate, isobutyrate, and 2-methylbutyrate concentrations decreased after the Mediterranean diet intervention [67]. No changes were observed in anthropometric or clinical measures between the Mediterranean diet and control diet groups [67]. Consumption of the Mediterranean diet decreased plasma TC, LDL cholesterol, and HDL cholesterol concentrations after 4 wk compared with the control [67]. The conversion of acetyl-CoA and enrichment in glutamate degradation to crotonyl-CoA correlated with the abundance of *F prausnitzii* [67]. Urolithin production negatively correlated with CRP, triglycerides, fat mass, body weight, BMI, and urinary carnitine concentrations [67]. However, no changes were observed in blood glucose, CRP, insulin, TMAO, or markers of metabolic disease including glucagon, ghrelin, gastric inhibitory peptide, GLP-1, leptin, c-peptide, resistin, visfatin, or plasminogen activator inhibitor 1 concentrations in either group [67].

In the study by Holscher et al. [49], healthy participants ($N = 18$) consumed isocaloric diets containing 0 g (control) or 42 g/d of walnuts for two 3-wk periods with a 1-wk washout in between conditions. The walnut treatment resulted in a higher relative abundance of *Faecalibacterium* sp than that in the control [49]. Fecal DCA and LCA concentrations were 25% and 45% lower, respectively, in the walnut group than those in the control [49]. Metabolic outcomes, including LDL cholesterol concentrations and noncholesterol sterol campesterol concentrations were 7% and 6% lower, respectively, following walnut consumption than those after the control [49]. *Faecalibacterium* sp. relative abundance was not associated with fecal secondary bile acid concentrations or TC or LDL cholesterol concentrations [49].

The dietary interventions used in these 5 studies were similar, and they used sources of dietary fiber as treatments or as part of a meal [39,49,65–67]. Thompson et al. [65] and Wan et al. [39] (low-fat diet intervention) provided a similar fat macronutrient profile. Both Wan et al. [39] (moderate-fat diet intervention) and Holscher et al. [49] provided a similar carbohydrate macronutrient profile. Meslier et al. [67] and Holscher et al. [49] reported reductions in fecal DCA and LCA concentrations. Thompson et al. [65] and Meslier et al. [67] observed decreases in fecal CDCA concentrations. Meslier et al. [67], Wan et al. [39], and Holscher et al. [49] reported decreases in LDL cholesterol concentrations. Moreover, Wan et al. [39] and Meslier et al. [67] observed decreases in TC and HDL cholesterol concentrations. The 5 studies reviewed that reported dietary interventions that enriched *Faecalibacterium* sp. reported positive metabolic outcomes, including effects on blood cholesterol and fecal bile acid concentrations. Correlational analyses revealed mixed findings for associations with *Faecalibacterium* spp and bacterial metabolites: 3 studies reported no relations [65,66,49], whereas a fourth reported a positive relationship between *Faecalibacterium* spp and fecal butyrate concentrations [39]. There were no reported associations between *Faecalibacterium* or microbial metabolites and physiologic outcomes.

Roseburia species

Roseburia spp. are anaerobic, gram-positive slightly curved rods equipped with flagella to facilitate their movement and colonization of the mucus lining [68,69]. These species are within the Bacillota (previously Firmicutes) phylum and are known for their ability to ferment xylan and β-mannans from the diet and produce SCFA, especially butyrate [68–72]. Because of their ability to ferment these fibers and produce butyrate as a terminal product, *Roseburia* spp. have anti-inflammatory and homeostatic properties [68–70]. A decrease in the abundance of *Roseburia* spp has been observed in patients with GI and metabolic diseases [68–70]. Interestingly, humans with type 2 diabetes mellitus who received fecal transplants from lean adults had improved insulin sensitivity, independent of weight loss, and increased butyrate-producing bacteria, including *Roseburia* spp [73].

The studies reporting an enrichment of *Roseburia* spp are outlined in Table 7 [30,43,49,67,74]. In the first study by Faits et al. [74], men and postmenopausal women ($N = 11$) consumed three 4.5-wk diets (simple carbohydrates, refined carbohydrates, and unrefined carbohydrates) with 2-wk washout periods in between each condition. All diets contained carbohydrates (60%), fat (25%), and protein (15%), with each differing in the type of carbohydrate consumed [74]. Consumption of unrefined carbohydrates led to a higher abundance of *Roseburia* sp. (11.3%) compared with simple carbohydrates [74]. There were no observed effects on fecal SCFA concentrations among all 3 groups [74]. There was a decrease in fecal bile acid concentrations after consumption of unrefined carbohydrates compared with those after simple carbohydrates [74]. Fecal concentrations of LCA decreased by 50% after consumption of unrefined carbohydrates compared with those after simple carbohydrates [74]. Further, fecal DCA concentrations decreased by 64% after consumption of unrefined carbohydrates compared with those after simple carbohydrates [74]. All groups had reductions in LDL cholesterol, non–HDL cholesterol, and TC concentrations [74]. The decreases in TC, LDL cholesterol, and non–HDL cholesterol concentrations were similar among the simple and unrefined carbohydrate groups; however, the refined carbohydrate group only had a slight reduction [74]. All groups had decreases in TC/HDL cholesterol and LDL cholesterol/HDL cholesterol ratios [74]. TC/HDL cholesterol and LDL cholesterol/HDL cholesterol ratio reductions were similar among the simple and unrefined carbohydrate groups; however, the refined carbohydrate group only had a slight decrease [74]. Correlational analyses among *Roseburia* spp, fecal metabolites, and metabolic outcomes were undertaken, revealing no associations among the variables [74].

In the study by Holscher et al. [49], healthy participants ($N = 18$) consumed isocaloric diets containing 0 g (control) or 42 g/d of walnuts for two 3-wk periods with a 1-wk washout in between conditions. The walnut treatment resulted in a higher relative

TABLE 7
Roseburia species.

Reference	Study design (duration/ washout duration)	Population characteristics/sample size, *N* (*n* intervention group)	Intervention (dosage)	Comparator (dosage)	Microbial metabolite(s)	Health measures	Results
[74]	Randomized, controlled, crossover (4.5 wk/2 wk)	Adults, males and postmenopausal females, age 65 ± 8 y, LDL cholesterol ≥2.6 mmol/L, BMI 29.8 ± 3.2/*N* = 11	Diets enriched with simple, refined, or unrefined carbohydrate-containing foods (60% carbohydrate, 25% fat, 15% protein)	NA	Fecal SCFA, fecal BA	Blood lipids, inflammatory markers, glycemic markers, anthropometric measurements	↑*Roseburia* ↓LCA ↓DCA ↓TC ↓LDL cholesterol ↓Non–HDL cholesterol ↓LDL cholesterol/HDL cholesterol ↓TC/HDL cholesterol
[67]	Randomized, Controlled Two-Armed, Parallel (8 wk/NA)	Adults with overweight and obesity, age ≥20y-≤65y, BMI ≥24/*N* = 82 (43)	Mediterranean diet (NA)	Habitual diet (NA)	Fecal SCFA, Fecal BCFA, Fecal BA, Urolithins	Blood lipids, Inflammatory markers, Glycemic markers, Hormones, Chemicals, Anthropometric measurements	↑*Roseburia* ↓Total BAs ↓DCA ↓LCA ↓CDCA ↓Valerate ↓Isovalerate ↓Isobutyrate ↓2-methylbutyrate ↑Urolithin glucuronides ↓TC ↓HDL cholesterol
[30]	Randomized, Controlled, Parallel, Multicenter (45 d/NA)	Mildly hypercholesterolemic adults, age <50 or ≥50 y, BMI <24 or ≥24/*N* = 187 (94)	Oats (80 g/d) containing β-glucan + 56.8 mg polyphenol	Rice (80 g/d)	Plasma SCFA	Blood lipids, Anthropometric measurements	↑*Rosburia* ↑Acetic acid ↑Propionic acid ↓TC ↓LDL cholesterol ↓Non–HDL cholesterol
[49]	Randomized, Controlled-Feeding, Crossover (3 wk/ 1 wk)	Healthy adults, age 35-67.8y, BMI 20.2-34.9/*N* = 18	Isocaloric diet + walnuts (42 g/d)	Isocaloric diet (NA)	Fecal BA	Blood lipids, Inflammatory markers, Glycemic markers, Noncholesterol sterol, Anthropometric measurements	↑*Roseburia* ↓DCA ↓LCA ↓LDL cholesterol ↓Noncholesterol sterol campesterol
[43]	Randomized, Controlled (8 wk/NA)	Females with overweight or obesity at cardiometabolic risk, 20-55 y, BMI ≥27 and <30, increased body fat (≥32%), increased waist circumference (≥80cm)/ *N* = 40 (25)	Brazil nuts (15g/d) + cashew nuts (30 g/d)	Free of nuts (−500 kcal/d)	Fecal SCFA	Blood lipids, Inflammatory markers, Glycemic markers, Intestinal permeability markers, Anthropometric measurements	↑*Roseburia* ↓Acetic acid ↑Propionic acid

Abbreviations: BA, bile acids; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; NA, not applicable; SCFA; short-chain fatty acid; TC, total cholesterol.

abundance of *Roseburia* spp than the control [49]. Fecal DCA and LCA concentrations were 25% and 45% lower, respectively, than those in the control [49]. At the end of the walnut treatment, *Roseburia* spp tended to be correlated with LCA concentrations [49]. Metabolic outcomes including LDL cholesterol concentrations and noncholesterol sterol campesterol concentrations were 7% and 6% lower, respectively, following walnut consumption than those after the control [49]. The relative abundance of fecal *Roseburia* spp was not associated with TC or LDL cholesterol concentrations at the end of the walnut consumption period [49].

In the study by Meslier et al. [67], sedentary participants with overweight and obesity and a low intake of fruit and vegetables consumed the Mediterranean diet isocaloric and were compared with those who followed their habitual diet [$n = 43$] or maintained their habitual diet [control; $n = 39$] for 8 wk [67]. Consumption of the Mediterranean diet increased levels of *Roseburia faecis* after 4 wk, *Roseburia hominis* after 8 wk and *Roseburia intestinalis* after 4 and 8 wk compared with the control [67]. In addition, consumption of the Mediterranean diet decreased fecal bile acid concentrations compared with the control [67]. Specifically, consumption of the Mediterranean diet reduced fecal DCA and LCA concentrations after 4 and 8 wk [67]. After 8 wk, there was a reduction in CDCA concentrations when comparing the Mediterranean diet with the control diet [67]. Urolithin urinary concentrations increased after consumption of the Mediterranean diet compared with that after the control [67]. No changes in fecal SCFA concentrations including acetate, propionate, and butyrate were observed following the Mediterranean diet intervention [67]. However, fecal BCFA concentrations including valerate, isovalerate, isobutyrate, and 2-methylbutyrate decreased after the Mediterranean diet intervention [67]. No changes were observed in anthropometric or clinical measures between the Mediterranean diet and control diet [67]. Consumption of the Mediterranean diet decreased plasma TC, LDL cholesterol, and HDL cholesterol concentrations after 4 wk compared with the control [67]. Urolithin production negatively correlated with CRP, triglycerides, fat mass, body weight, BMI, and urinary carnitine concentrations [67]. However, no changes were observed to blood glucose, CRP, insulin, TMAO, or markers of metabolic disease including glucagon, ghrelin, gastric inhibitory peptide, GLP-1, leptin, C-peptide, resistin, visfatin, or plasminogen activator inhibitor 1 concentrations in either group [67].

In the study by Xu et al. [30], participants with mild hypercholesterolemia not only consumed either oats containing 3 g of β-glucan and 56.8 mg polyphenol ($n = 94$) or control rice ($n = 93$) (80 g/d) but also maintained their habitual diet for 45 d [30]. Oat consumption significantly increased the abundance of *Roseburia* spp compared with the control [30]. Plasma acetic and propionic concentrations significantly increased following the oat intervention; however, similar trends were also seen in the control group [30]. There were no other significant effects found in either group for SCFAs [30]. In the oat group, *Roseburia* spp positively correlated with plasma butyric, propionic, and valeric acid concentrations and negatively correlated with isobutryic and hexenoic acid concentrations [30]. In the control group, *Roseburia* spp positively correlated with plasma butyric and valeric acid concentrations [30]. After the oat treatment, there were decreases in LDL cholesterol concentrations after days 30 (7.6%) and 45 (9.1%) [30]. In addition, *Roseburia* spp negatively correlated with HDL cholesterol concentrations in the oat group [30]. In both groups, TC, and non–HDL cholesterol concentrations decreased after days 30 (5.7%) and 45 (8.7%); however, the reduction in total and non–HDL cholesterol concentrations was greater in those who consumed oats than that in those who consumed the control [30].

In the study by Silveira et al. [43], female participants ($N = 40$) with overweight and obesity at cardiometabolic risk were assigned to energy-restricted groups: control group free of nuts (−500 kcal/d) or Brazil nut group (30 g of cashew nuts and 15 g of Brazil nuts per day) for 8 wk. In the 25 females who completed the study, consumption of Brazil nuts increased the relative abundance of *Roseburia* spp after 8 wk compared with the control group [43]. The Brazil nut group also experienced significant increases in fecal propionic acid concentrations compared with baseline; however, no differences were observed between groups [43]. Consumption of Brazil nuts significantly decreased acetic acid concentrations compared with the control [43]. Butyric acid and fecal pH did not change from baseline or between treatments [43]. Both groups, compared with baseline, saw reductions in weight loss, waist circumference, hip circumference, BMI, and body fat, but there were no differences between groups [43]. Regarding inflammatory markers, there were no changes observed in plasma concentrations of CRP, TNF, IL-6, IL-8, IL-10, and IL-17A [43]. Lactulose-to-mannitol ratio and mannitol excretion did not differ between treatments; however, the control group had higher lactulose excretion than the Brazil nut group [43]. Lactulose-to-mannitol ratio positively correlated with reductions in percentage of body fat and IL-8 concentrations [43]. Reductions in lactulose excretion positively correlated with reductions in percentage of body fat and BMI [43]. Changes in intestinal permeability correlated with a greater reduction in body fat percentage and IL-8 concentrations [43]. There were no reported correlations between *Roseburia* spp and physiologic measures [43].

The dietary interventions used in these 5 studies were similar and provided sources of dietary fiber as treatments or as part of a meal [30,43,49,67,74]. Interestingly, Faits et al. [74], Meslier et al. [67], Xu et al., and Silveira et al. [43] reported no effects on fecal SCFA concentrations. Faits et al. [74], Meslier et al. [67], and Holscher et al. [49] observed reductions in fecal DCA and LCA concentrations. All studies but 1 [43] reported decreases in LDL cholesterol concentrations [30,49,67,74]. Faits et al. [74], Meslier et al. [67], and Xu et al. [30] observed decreases in TC and HDL cholesterol concentrations [30,67,74]. In addition, Faits et al. [74] and Xu et al. [30] reported decreases in non–HDL cholesterol concentrations [30,74]. Meslier et al. [67] and Silveira et al. [43] reported no effects on CRP concentrations. Although 4 studies [30,43,67,74] reported no changes in fecal SCFA concentrations, positive metabolic health outcomes related to cholesterol and bile acid absorption were frequently observed, which could be correlated with the increase in *Roseburia* spp as it is known for its ability to produce butyrate. Only 1 study [30] reported a statistically significant association between *Roseburia* and a health marker—Xu et al. reported that *Roseburia* spp negatively correlated with HDL cholesterol concentrations in the oat group. Correlational analyses among *Roseburia* spp, fecal metabolites, and metabolic outcomes were undertaken in 3 other studies [43,49,74], revealing no associations between the variables.

Ruminococcus species

Although initially identified in bovine rumen, *Ruminococcus* spp have since been detected in various animal hosts [75,76]. These anaerobic gram-positive cocci play a significant role in breaking down resistant starches within the GI tract. These starches are vital for their growth, and because of fermentation, they produce metabolites that can be further fermented by other microorganisms in the gut to create SCFA, mainly butyrate and propionate. This process plays a critical part in energy production, digestion, and gut homeostasis and helps to reduce inflammation and infections, ultimately leading to a mutually beneficial relationship between the host and *Ruminococcus* spp [76,77]. *Ruminococcus* sp. has been shown to reverse infectious diarrhea and are associated with reduced risk of type 2 diabetes mellitus and colon cancer in human patients [76].

Results of studies reporting an enrichment of *Ruminococcus* spp are reported in Table 8 [43,78]. In the study by Hughes et al. [78], healthy participants consumed resistant starch type 2–enriched wheat rolls (14–19 g/d; $n = 15$) or control wild-type wheat rolls (2–3 g/d; $n = 15$) for 7 d with a 2-wk washout period in between conditions [78]. Consumption of resistant starch type 2 increased the proportion of *Ruminococcus* spp compared with baseline and control group [78]. Fasting breath hydrogen and methane concentrations increased after resistant starch type 2 consumption compared with those after the control [78]. Regarding fecal SCFA concentrations, no significant changes were observed, and SCFA concentrations were very low among all groups [78]. In addition, fecal pH concentrations were not influenced by resistant starch type 2 consumption compared with those by the control [78]. Consumption of resistant starch type 2 decreased postprandial glucose and insulin concentrations compared with the control [78]. In addition, peak glucose and insulin concentrations decreased following resistant starch type 2 consumption compared with those after the control [78]. There were no changes to HOMA-IR, fasting glucose, or insulin concentrations in either group [78]. *Ruminococcus* spp positively correlated with methane production iAUC and fecal butyrate concentrations, but was not significant compared with those of the control [78]. There was a positive correlation between fasting breath hydrogen and both relative and absolute fecal butyrate concentrations [78]. In addition, breath hydrogen iAUC positively correlated with absolute fecal butyrate concentrations [78]. However, breath hydrogen iAUC concentrations negatively correlated with relative fecal acetate concentrations [78]. There were positive correlations between fecal propionate and fasting glucose concentrations, as well as fecal butyrate concentrations and glucose iAUC [78].

In the study by Silveira et al. [43], female participants ($N = 40$) with overweight and obesity at cardiometabolic risk were assigned to energy-restricted groups: control group free of nuts (−500 kcal/d) or Brazil nut group (30 g of cashew nuts and 15 g of Brazil nuts per day) for 8 wk. In the 25 females who completed the study, consumption of Brazil nuts increased the relative abundance of *Ruminococcus* spp after 8 wk compared with the control diet [43]. The Brazil nut group also exhibited significant increases in fecal propionic acid concentrations compared with those at baseline; however, there was no differences observed between groups [43]. Consumption of Brazil nuts decreased acetic acid concentrations compared with the control [43]. Butyric acid and fecal pH did not significantly change from baseline or between treatments [43]. Both groups, compared with baseline, saw reductions in weight loss, waist circumference,

TABLE 8
Ruminococcus species.

Reference	Study design (duration/ washout duration)	Population characteristics/ sample size, *N* (n intervention group)	Intervention (dosage)	Comparator (dosage)	Microbial metabolite(s)	health Measures	Results
[78]	Randomized, double-blind, placebo-controlled, crossover (1 wk/2 wk)	Healthy adults, 40–65 y, BMI >18.5 or <39.9/ *N* = 30 (15)	RS2-enriched wheat rolls (14–19 g/d)	Wild-type wheat rolls (2–3 g/d)	Fecal SCFA, breath methane, fasting methane, breath hydrogen, fasting hydrogen	Glycemic markers, anthropometric measurements	↑*Ruminococcus* ↑Fasting breath hydrogen ↑Fasting breath methane ↓Postprandial glucose ↓Peak glucose ↓Postprandial insulin ↓Peak insulin
[43]	Randomized, controlled (8 wk/NA)	Females with overweight or obesity at cardiometabolic risk, 20–55 y, BMI ≥27 and <30, increased body fat (≥32%), increased waist circumference (≥80 cm)/*N* = 40 (25)	Brazil nuts (15 g/ d)+cashew nuts (30 g/d)	Free of nuts (−500 kcal/d)	Fecal SCFA	Blood lipids, inflammatory markers, intestinal permeability markers, glycemic markers, anthropometric measurements	↑*Ruminococcus* ↑Propionic acid ↓Acetic acid

Abbreviations: NA, not applicable; RS2, resistant starch type 2; SCFA; short-chain fatty acid.

hip circumference, BMI, and body fat, but there were no differences between groups [43]. Regarding inflammatory markers, there were no changes observed in plasma concentrations of CRP, TNF, IL-6, IL-8, IL-10, and IL-17A [43]. Lactulose-to-mannitol ratio and mannitol excretion did not differ between treatments; however, the control group had higher lactulose excretion than the Brazil nut group [43]. Lactulose-to-mannitol ratio positively correlated with reductions in percentage of body fat and IL-8 concentrations [43]. Reductions in lactulose excretion positively correlated with reductions in percentage of body fat and BMI [43]. Changes in intestinal permeability correlated with a greater reduction in body fat and IL-8 concentrations and increases in the abundance of *Ruminococcus* spp [43].

Both studies used sources of dietary fibers as treatment methods [43,78]. Interestingly, Hughes et al. [78] and Silveira et al. [43] reported no effects on fecal SCFA concentrations. Even though *Ruminococcus* spp. typically produces SCFA, studies included did not observe any changes to fecal SCFA concentrations [43,78]; however, although there was not a main effect of treatment on SCFA, Hughes et. al [78] did report a positive association between the abundance of *Ruminococcus* spp and fecal SCFA concentrations. This may be due to the possibility that SCFA produced by *Ruminococcus* spp. could be used by other bacteria or other metabolic processes in the body. Specific to physiologic measures, Silveira et al. [43] reported correlations among body fat, IL-8 concentrations, and the abundance of *Ruminococcus* spp, whereas Hughes et al. [78] reported positive associations between fecal SCFA and fasting glucose as well as glucose iAUC.

Conclusions and Future Directions

The objective of this review was to summarize the available literature on dietary approaches that enriched bacteria within the human intestinal microbiota that may serve as potential next-generation probiotics or targets for enrichment via next-generation prebiotics. Specifically, we aimed to summarize the literature on dietary approaches that can enrich Akkermansia, *Bacteroides*, *Clostridium*, *Eubacterium*, *Faecalibacterium*, *Roseburia*, and *Ruminococcus* species in randomized controlled nutrition trials in healthy adults that characterized microbiota, metabolome, and GI, metabolic, and cognitive health outcomes. Our findings revealed that a range of dietary approaches enriched these microbes and had varying effects on the metabolome, as well as associations with physiologic measures. A similarity among these dietary approaches was that many provided supplemental fibers (i.e., fructo-oligosaccharides, galacto-oligosaccharides, resistant starch type 2, inulin-propionate ester, yeast mannan, and high-amylose maize starch) or foods rich in fiber (i.e., Brazil nuts, cashew nuts, walnuts, avocados, oats, and raspberries). As dietary fiber cannot be broken down by human digestive enzymes, it is a substrate for select microorganisms, including the 7 bacteria studied in this study. Similarly, several of these studies provided sources of unsaturated fatty acids (i.e., Brazil nuts, cashew nuts, walnuts, avocados, and a Mediterranean Diet pattern), which may affect bile acid profiles, with subsequent effects on the microbiota and health. Likewise, many studies reviewed provided sources of phytonutrients as dietary interventions (i.e., FruitFlow—a water-soluble tomato extract, raspberries, mushrooms, avocados, Brazil nuts, cashew nuts, and a Mediterranean Diet pattern). Polyphenols and their metabolites have been shown to exert prebiotic-like effects on the intestinal microbiome [79]. In addition, certain phytonutrients, such as berries, have been linked to anti-inflammatory effects and, in turn, reducing gut inflammation [80]. Some health benefits reported in these studies, which may be partially underpinned by the microbiota, included improved lipid profiles, insulin sensitivity, and GI symptoms. We were not able to report on biotic-enriching dietary approaches that benefit cognitive health because the studies investigating cognitive health outcomes were excluded because the population included adults with diagnosed disease(s) and/or did not include statistical approaches to determine the differences among study conditions. Overall, the studies in this systematic review revealed differential effects of dietary interventions on bacterial enrichment and bacterial metabolite concentrations, with some associations among bacteria, metabolites, and physiological responses.

This systematic review focused on microbes with varying degrees of interest for their potential as next-generation probiotics or targets for enrichment within the autochthonous intestinal microbiota. However, it should be noted that although *Akkermansia, Bacteroides, Clostridium, Eubacterium, Faecalibacterium, Roseburia, and Ruminococcus* species are generally considered commensal intestinal microorganisms, each can still have detrimental effects on the host in certain circumstances. Depending on the context of the human health conditions and diet, the same microorganism can interact differently with the host—for example, although there are many studies indicating that *Akkermansia* spp. are an intestinal symbiont that improves health [81], in studies where mice were fed diets deficient in dietary fiber, *Akkermansia* spp eroded intestinal mucus, thereby increasing susceptibility to pathogenic infections [82].

A key limitation of the research summarized in this report is that the connections between the microbes, metabolites, and physiologic responses were correlative, not causative. Indeed, most clinical research on diet-microbiota–health connections remains correlative. Future work coupling animal and in vitro research and advanced analytic approaches is needed to delineate the independent and interactive effects of diet, microbes, and metabolites so that causative connections between specific microbes or microbial metabolites and human physiology can be determined. Research studies that combine experimental and statistical approaches are needed to advance the field. For example, reverse translation experimental studies [83] and mediation analyses [84,85] can help establish if connections between diet, gut microbiota, and physiologic markers of health are causal.

Continued research on this topic using state-of-the art bioinformatic technologies, next-generation sequencing, and culturomics will help to fill the gap in knowledge on the interconnections among diet, the microbiota, and health so that specific microbes can be targeted either within the autochthonous intestinal microbiota or as next-generation probiotics. Tools that allow for further integration of dietary and microbiome data, such as DIETDiverR [86], will also help scientists to better understand the dietary patterns, foods, and nutrients underlying diet-microbiota connections, which has implications for the expansion of substrates accepted as prebiotics. Integrative approaches that build upon human studies to mechanistically

characterize the effects of the microorganisms understudy using animal and in vitro models will improve the ability to draw complete findings on this topic. Finally, the importance of study design and statistical modeling must not be overlooked—approaches that allow for causative inferences to be made are vital for delineating diet-microbiota–health connections.

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Author contributions

The authors' responsibilities were as follows – VKH and HDH: were responsible for establishing the scope and objective of the manuscript; VKH: devised and executed the literature search and performed the initial screenings; VKH and NMV: reviewed the remaining publications with input from HDH; VKH and NMV were responsible for the construction of data tables and writing the first draft of the manuscript; HDH: reviewed and critically edited the manuscript; and all authors: read and approved the final manuscript.

Conflict of interest

HDH is a member of *The Journal of Nutrition* Editorial Board. All other authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2024.10.043.

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