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Prebiotic effect of dietary polyphenols: A systematic review

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ABSTRACT

Prebiotics are substrates selectively metabolized by hindgut microorganisms conferring health benefits. Recent studies suggest polyphenols as candidate to prebiotics. Thus, this systematic review aimed to investigate the prebiotic effect of dietary polyphenols in preclinical and clinical studies. Animal studies demonstrated that the consumption of polyphenols, especially catechins, anthocyanins and proanthocyanidins, increases the abundance of *Lactobacillus*, *Bifidobacterium*, *Akkermansia*, *Roseburia*, and *Faecalibacterium* spp. Moreover, polyphenols supplementation increased the production of short-chain fatty acids (SCFA), including butyrate. The included clinical trials showed an increased abundance of *Lactobacillus acidophilus*, *Bifidobacterium* and *Faecalibacterium* spp., and a reduction in plasma lipopolysaccharide-binding protein after the consumption of anthocyanins and ellagic acid. In conclusion, there is strong evidence in preclinical studies that dietary polyphenols can stimulate both the growth of microorganisms identified as prebiotic targets and an increase in the production of SCFA. Therefore, clinical trials are warranted to investigate the prebiotic effect of dietary polyphenols on humans.

1. Introduction

Prebiotics are defined as substrates selectively utilized by the host's microorganisms resulting in benefits for metabolic health, gastrointestinal system, bone health and mental health. Some dietary fibers, especially resistant oligosaccharides (inulin, fructo-oligosaccharides and galacto-oligosaccharides), are well-recognized in literature as prebiotics (Gibson et al., 2017). Besides dietary fibers, recent studies have shown the interaction between polyphenols and the gut microbiota, suggesting them as candidate compounds to prebiotics (Sanders, Merenstein, Reid, Gibson, & Rastall, 2019; Shortt et al., 2018; Singh, Cabral, Kumar, Ganguly, & Pandey, 2019).

Polyphenols are secondary metabolites of plants, characterized by aromatic rings bearing one or more hydroxyl groups in their chemical structure, ranging from that of a simple phenolic molecule to that of a complex high-molecular mass polymer (Mojzer et al., 2016). These compounds have low bioavailability and extensive metabolism in the large intestine, favoring interactions with intestinal microorganisms (Bian, Wei, Zhao, & Li, 2020). Actually, there is a bidirectional interaction, in which polyphenols modulate the gut microbiota and, conversely, microorganisms can modulate the activity of the phenolic compounds. This interaction can regulate the metabolism and the bioavailability of polyphenols, converting them into metabolites, which may have different effects on the host health (Singh et al., 2019).

Dietary polyphenols are associated with a reduced risk of cardiometabolic diseases when regularly consumed (Noad et al., 2016). Studies show that polyphenols have antioxidant, anti-inflammatory (Chai, Davis, Zhang, Zha, & Kirschner, 2019), anti-obesogenic, antilipidemic (Fang et al., 2019) and anti-diabetic (Paquette et al., 2017) activities. However, the role of dietary polyphenols in health largely depends on their metabolism, absorption and bioavailability processes which are, in turn, related to the gut microbiota modulation, in terms of composition and functionality. Although polyphenols are currently recognized as modulators of the gut microbiota composition, there is still no conclusive evidence of their prebiotic effect (Cueva, Silva, Pinillos, Bartolomé, & Moreno-Arribas, 2020). The prebiotic effect of each polyphenol can be influenced by the food source and the chemical structure of the compound, along with the individual differences in the gut microbiota composition (Serreli & Deiana, 2019). Therefore, establishing a relationship among the polyphenols consumption, the growth of microorganisms recognized as prebiotic targets, the metabolites generated and the effect on health is somewhat of a challenge. This systematic review aimed to investigate the available evidence of the prebiotic effect of dietary polyphenols.

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Table 1
Detailed search terms in the databases (August 2, 2019).

Database	Search term	N° of items found (total = 4025)
PubMed	(polyphenols[MeSH Terms] or flavonoids [MeSH Terms] or tannins [MeSH Terms] or lignans [MeSH Terms] or stilbenes [MeSH Terms] or curcumin [MeSH Terms] or "phenolic acids" [Title/Abstract]) AND (microbiota [MeSH Terms] or "human microbiome" [MeSH Terms] or "gut microbiota" [Title/Abstract] or "gut microbiome" [Title/Abstract] or prebiotic [MeSH Terms] or firmicutes [Title/Abstract] or bacteroidetes [MeSH Terms])	796
Scopus	(TITLE-ABS-KEY ((polyphenols OR flavonoids OR tannins OR lignans OR stilbenes OR curcumin OR "phenolic acids")) AND TITLE-ABS-KEY ((microbiota OR "human microbiome" OR "gut microbiota" OR "gut microbiome" OR prebiotic OR firmicutes OR bacteroidetes)))	1633
Web of Science	#1 TS = (polyphenols OR flavonoids OR tannins OR lignans OR stilbenes OR curcumin OR "phenolic acids") AND #2 TS = (microbiota OR "human microbiome" OR "gut microbiota" OR "gut microbiome" OR prebiotic OR firmicutes OR bacteroidetes)	1596

2. Material and methods

2.1. Search strategy and study selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015), a systematic literature search was carried out through the PubMed, Scopus and Web of Science databases up to August 02, 2019, using terms related to prebiotic, gut microbiota and polyphenols (Table 1). After the removal of duplicates using a bibliographic reference manager, two authors independently reviewed the titles and abstracts of each paper identified in the search. This procedure was performed using a systematic review software. The selected studies were retrieved for full-text analysis and eligible articles were identified. Afterwards, they were reanalyzed for details of the study design and their outcome to select the papers included in this review. Any disagreements in this regard were solved by the means of discussion with a third author.

2.2. Inclusion and exclusion criteria

The following criteria were applied for inclusion: (1) a randomized controlled study design using animals and/or humans; (2) intervention with either isolated polyphenol or food extract; (3) phenolic compounds profile of the food extract available; (4) outcomes related to changes in the gut microbiota composition, with stimulation of microorganisms recognized as prebiotic targets (*Lactobacillus, Bifidobacterium, Roseburia, Eubacterium,* and *Faecalibacterium* spp.) (Gibson et al., 2017), including the *Akkermansia* spp. (Sanders et al., 2019), and/or an increase in the production of short-chain fatty acids (SCFA), including butyrate; and (5) publishing in English. Studies with a lower than eight number of animals per group, acute studies, drug-induced pathologies, gut microbiota composition assessment by culture plate methods, and without the microorganism genera identification were excluded.

2.3. Data extraction

The included studies were reviewed and the following data were abstracted: sample source, exposure dosage, animal model or study population (subjects and sample size), intervention period, diet type, outcomes related to gut microbiota and host health, paper's first author and date of publication.

2.4. Quality assessment

The quality assessment of animal studies was conducted using the SYRCLE's risk of bias tool (Hooijmans et al., 2014). Cochrane Collaboration's tool (Higgins et al., 2011) was used for the quality assessment of clinical trials.

3. Results

3.1. Description of studies

The initial search strategy yielded 4025 articles, out of which 1685 were excluded as duplicates. After analysis of titles and abstracts, 2044 records were excluded, including *in vitro* studies, review articles, conference abstracts, letters, protocols, editorials, and unavailable full-texts, and 296 were selected for full-text review. Among these, 242 studies were excluded according to the exclusion criteria. Thus, full-text review of 54 eligible studies were made, excluding 30 articles for different reasons: there was no growth of microorganisms recognized as prebiotic targets (Casanova-Marti et al., 2018; Cheng, Chen, Zhang, et al., 2019; Cires et al., 2019; Collins et al., 2016; Cowan et al., 2014; González-Sarrías et al., 2017; Griffin et al., 2017; Guo, Tang, et al., 2018; Li, Liu, Liu, Liao, & Zou, 2019; Most, Penders, Lucchesi, Goossens, & Blaak, 2017; Porras et al., 2017; Remely et al., 2017; Shen, Wan, Wang, & Jiang, 2019; Sung et al., 2017; Tan et al., 2018; Unno & Osakabe, 2018; Wang et al., 2019; Yu et al., 2019; Yuan et al., 2018; Zhang, Dong, et al., Zhang, Zhang, et al., 2018; Zhang, Wu, Li, Xin, & Liu, 2019; Zhou, Zhang, Arikawa, & Chen, 2019); there was no increase in the production of butyrate (Ginés et al., 2019; Grzelak-Błaszczyk et al., 2018; Zhou, Tang, Shen, & Wang, 2018); and extracts contained other compounds such as oligosaccharides, polysaccharides or dietary fiber (Chiu et al., 2017; Gao et al., 2018; Garcia-Mazcorro et al., 2018; Romo-Vaquero et al., 2014). Finally, 24 articles (22 animal studies and 2 clinical trials) fulfilled the eligibility criteria and were included in this systematic review (Fig. 1). The animal studies were organized into two sections, according to polyphenol classes and considering the majority compound of the polyphenols profile available in the studies: flavonoids and other polyphenols (lignans, phenolic acids, stilbenes and vanillin) (Table 2). Data on the polyphenol class and subclass were extracted from the Phenol-Explorer database (www.phenol-explorer.eu).

3.2. Prebiotic effect of dietary polyphenols

3.2.1. Animal studies

3.2.1.1. Flavonoids. The flavonoids were the most investigated phenolic compounds in relation to the effects on the gut microbiota composition and the benefits to the host health. Prebiotic effect of anthocyanins, a subclass of the flavonoids, was evaluated in three animal studies (Anhê et al., 2018; Li, Wu, et al., 2019; Van Hul et al., 2018). In a study with Arctic berry extracts (Anhê et al., 2018), and another with cinnamon bark and grape pomace extracts (Van Hul et al., 2018), the most abundant polyphenols present in the extracts were anthocyanins and proanthocyanidins. However, the authors associated the main outcomes with the presence of the proanthocyanidins. The proanthocyanidins or procyanidins effects on the gut microbiota were investigated in other three studies. A marked increase in the abundance of *Akkermansia* was observed after the consumption of polymeric

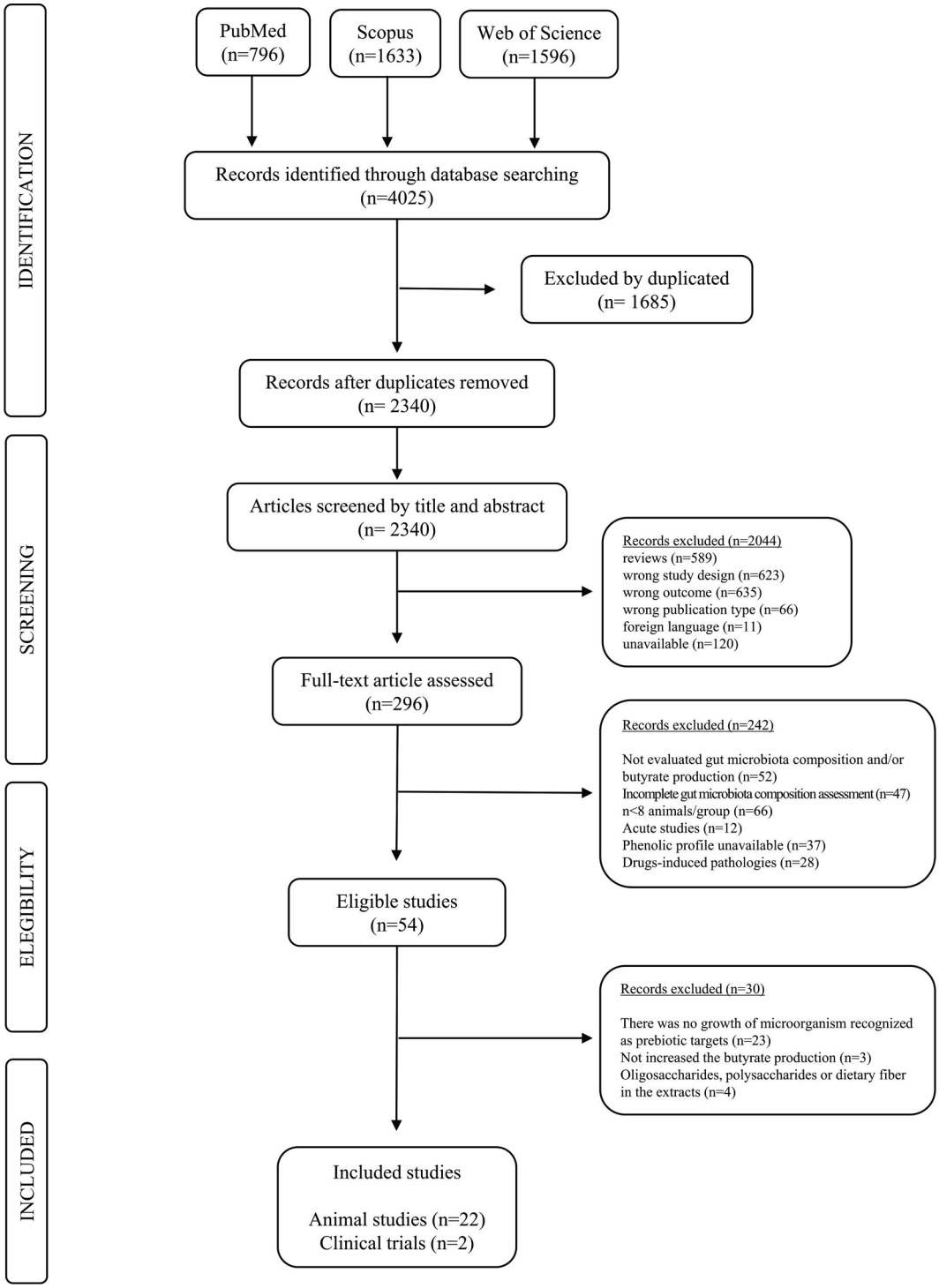

Fig. 1. Flowchart of the systematic review.

procyanidins from apple (Masumoto et al., 2016), and cranberry extract rich in proanthocyanidins (Anhê et al., 2015, 2017). Moreover, body weight gain reduction, insulin sensitivity improvement, upregulation of genes involved in lipid catabolism, and downregulation of pro-inflammatory genes in the liver were the health benefits associated with the consumption of proanthocyanidins (Anhê et al., 2015, 2017; Masumoto et al., 2016).

The prebiotic effect of the flavanols (epigallocatechin gallate, epigallocatechin, epicatechin gallate, epicatechin), a flavonoid subclass, was characterized in seven animal studies. The main food sources investigated were green tea, black tea, oolong tea, and Pu-erh tea. The intervention doses were very different among studies, and intervention periods ranged from 28 to 196 days (Dey et al., 2019; Henning et al., 2018; Liu et al., 2019; Lu et al., 2019; Ma et al., 2019; Wang et al., 2018; Xia et al., 2019). An increase in the abundance of *Akkermansia* and *Bifidobacterium* was observed in mice fed a high-fat diet after the consumption of green tea polyphenols (Dey et al., 2019; Ma et al., 2019; Wang et al., 2018). Supplementation of the oolong tea extract and decaffeinated black tea extract increased the butyrate production (Liu et al., 2019; Henning et al., 2018), while the Pu-erh tea extract consumption stimulated the *Akkermansia* and *Roseburia* growth (Lu et al., 2019; Xia et al., 2019).

Table 2
Characteristics of included studies on prebiotic effect of dietary polyphenols (n = 24).

Compound (food)	Dose	Animal/Human	Study design		Main outcome		Reference
			Period (days)	Diet	Gut microbiota	Health	
			Animal studies				
Flavonoids							
Anthocyanins (bilberry extract)	10, 20 or 40 mg extract/kg bw/day (IG)	Sprague-Dawley rats (n = 10/group)	70	STD	↑ *Lactobacillus* ↑ cecal SCFA ↓ *Firmicutes/Bacteroidetes* ratio	↓ digestive enzymes activity	Li, Wu, et al. (2019)
Anthocyanins and proanthocyanidins (Arctic berry extracts)	200 mg extract/kg bw/day (water)	Male C57BL/6J mice (n = 12/group)	56	HFHS	↑ *Akkermansia muciniphila* (NS) cecal SCFA	↑ insulin sensitivity	Anhê et al. (2018)
Anthocyanins (grape pomace extract) and proanthocyanidin A (cinnamon bark extract)	grape pomace: 2 g extract/kg diet cinnamon bark: 8.2 g extract/kg diet	Male C57BL/6J mice (n = 14/group)	56	HFD	↑ *Roseburia* (NS) cecal SCFA	↓ fat mass gain ↓ liver steatosis	Van Hul et al. (2018)
Catechins (green tea extract)	2% of extract (diet)	Male C57BL/6J mice (n = 10/group)	56	HFD	↑ *Bifidobacterium* and *Akkermansia muciniphila* ↓ *Firmicutes/Bacteroidetes* ratio	↓ adiposity	Dey et al. (2019)
Catechins (green tea polyphenols)	0.05, 0.2 or 0.8% of tea polyphenols (diet)	HFA C57BL/6J mice (n = 8/group)	56	HFHS	↑ fecal acetate and butyrate ↓ *Firmicutes/Bacteroidetes* ratio	↓ bw gain ↓ serum lipid profile, glucose and insulin	Wang et al. (2018)
Catechins (green tea polyphenols)	100, 200 or 400 mg of green tea polyphenols/kg bw/day (IG)	SPF C57BL/6 mice (n = 8/group)	84	HFD	↑ *Bifidobacterium*, *Akkermansia*, *Roseburia* (the highest dose)	↑ expression of hepatic lipid metabolism genes	Ma et al. (2019)
Catechins and caffeine (green tea, black tea and oolong tea water extracts)	1% tea extract (diet)	Male C57BL/6J mice (n = 12/group)	196	HFD	↑ fecal SCFA (oolong tea) ↓ plasma LPS	↑ glucose tolerance ↓ bw gain	Liu et al. (2019)
Catechins (decaffeinated green and black tea polyphenol extracts)	0.5 g extract/100 g diet	Male C57BL/6J Mice (n = 12/group)	28	HFHS	↑ fecal propionate and butyrate (black tea) ↓ *Firmicutes* ↑ *Bacteroidetes*	Induced bw loss	Henning et al. (2018)
Catechins (ripened Pu-erh tea extract)	0.1, 0.2, or 0.4% of extract (water)	Male C57BL/6N mice (n=10/group)	56	HFD	↑ *Roseburia* and *Akkermansia* ↓ *Firmicutes/Bacteroidetes* ratio ↓ serum LPS	↓ bw gain and metabolic endotoxemia	Lu et al. (2019)
Catechins and caffeine (aqueous raw and ripe Pu-erh tea extracts)	0.15 or 0.4 mg extract/kg bw/day (diet)	Male Wistar rats (n=18/group)	77	HFHS	↑ *Akkermansia muciniphila* ↑ *Firmicutes* ↓ *Bacteroidetes*	↑ glycolysis	Xia et al. (2019)
Genistein	3 mg/kg bw/day (diet)	Male C57BL6 mice (n=8/group)	180	HFD	↑ *Faecalibacterium* ↓ serum LPS	↓ serum triglycerides	López et al. (2018)
Hydroxysafflor yellow A	200 mg/kg bw/day (IG)	SPF C57BL/6J mice (n=8/group)	84	HFD	↑ *Akkermansia* ↑ cecal SCFA ↓ *Firmicutes/Bacteroidetes* ratio	↓ inflammation	Liu et al. (2018)
Isoflavones (soy extract)	150 or 450 mg extract/kg bw/day (diet)	Male Sprague Dawley rats (n=16/group)	91	HFD	↑ *Faecalibacterium* ↑ fecal butyrate and ↓ serum LPS ↓ *Firmicutes/Bacteroidetes* ratio	↓ oxidative damage and inflammation	Luo et al. (2019)
Naringenin (*S. chinensis* pollen extract)	7.86 or 15.72 g extract/kg bw/day (IG)	Male C57BL/6 mice (n=12/group)	112	HFD	↑ *Lactobacillus*	↓ fasting blood glucose	Cheng, Chen, Liu, Zhao, and Cao (2019)

(*continued on next page*)

Table 2 (*continued*)

Compound (food)	Dose	Animal/Human	Study design		Main outcome		Reference
			Period (days)	Diet	Gut microbiota	Health	
Polymeric and oligomeric procyanidin (apple)	0.5% procyanidins (diet)	C57BL/6J male mice (n = 10/group)	140	HFHS	↑ *Akkermansia* (eight times) ↓ *Firmicutes/Bacteroidetes* ratio ↓ serum LPS	Attenuate bw gain	Masumoto et al. (2016)
Proanthocyanidin (cranberry extract)	200 mg extract/kg bw/day (water)	Male C57Bl/6J mice (n = 8–11/group)	147	HFHS	↑ *Akkermansia muciniphila* ↓ *Firmicutes/Bacteroidetes ratio*	↑ insulin sensitivity	Anhê et al. (2017)
Proanthocyanidin (cranberry extract)	200 mg extract/kg bw/day (IG)	Male C57Bl/6J mice (n = 12/group)	56	HFHS	↑ *Akkermansia* spp. ↓ plasma LPS	↓ bw gain ↑ insulin sensitivity	Anhê et al. (2015)
Other polyphenols							
Lignans - syringaresinol	10 or 50 mg/kg bw/day (diet)	Male C57BL/6 mice (n = 12/group)	70	STD	↑ *Lactobacillus* and *Bifidobacterium* ↓ serum LPS-binding protein	↑ immune system	Cho et al. (2016)
Phenolic acids - dicaffeoylquinic acids (*Ilex kudingcha)*	3.3 or 10 mg/mouse (IG)	SPF male C57BL/6 mice (n = 8/group)	56	HFD	↑ *Bifidobacterium* and *Akkermansia* ↓ serum LPS	↓ inflammation	Xie et al. (2019)
Stilbenes - pterostilbene	15 mg/kg bw/day (IG)	Zucker (*fa/fa*) rats (n = 10/group)	42	STD	↑ *Akkermansia muciniphila* ↓ *Firmicutes*	↑ insulin sensitivity	Etxeberria et al. (2017)
Stilbenes - resveratrol	200 mg/kg bw/day (diet)	Male Kunming mice (n = 8/group)	84	HFD	↑ *Lactobacillus* and *Bifidobacterium* ↓ *Firmicutes* ↑ *Bacteroidetes*	↓ bw ↓ blood glucose and lipid	Qiao et al. (2014)
Other polyphenols - vanillin	0.1% diet	Male C57BL/6J mice (n = 7–8/group)	98	HFD	↓ *Firmicutes* ↑ cecal SCFA	↑ insulin sensitivity ↓ inflammation	Guo, Han, Zhan, You, and Huang (2018)
			Clinical trials				
Anthocyanins (wild blueberry drink)	25 g/250 mL água	20 healthy male individuals	crossover, placebo controlled (6 weeks)		↑ *Lactobacillus acidophilus* ↑ *Bifidobacterium* spp.	NR	Vendrame et al. (2011)
Punicalagins and ellagic acid (pomegranate extract)	0.45 g or 1.8 g extract (capsules)	49 overweight-obese subjects (mild hyperlipidemia)	double-blind, crossover, placebo controlled (9 weeks)		↑ *Faecalibacterium* ↓ plasma LBP	NR	González-Sarrías et al. (2018)

bw: body weight, SCFA: short-chain fatty acids, STD: standard, chow and normal diet, HFD: high-fat diet, HFHS: high-fat/high-sucrose diet, IG: intragastric, LPS: lipopolysaccharides, HFA: human flora-associated, SPF: specific-pathogen-free, (NS): not significant or not affected, NR: not reported, LBP: lipopolysaccharide-binding protein, ↑ and ↓: increase and decrease in the specific parameter, respectively.

The intervention with soy isoflavone extract containing 51% daidzin, 30% glycitin and 9% genistein increased the abundance of *Faecalibacterium* and the fecal butyrate content in obese rats, and improved intestinal barrier function through increasing the expressions of zonula occludens 1 (ZO-1), occludin and mucin 2 (Muc-2) genes (Luo et al., 2019). An increase of the *Faecalibacterium* genus was also observed after the consumption of genistein (López et al., 2018).

The effects of other flavonoid subclasses were investigated in two studies, in which the intervention samples were hydroxysafflor yellow A (HSYA) (Liu et al., 2018) and *Schisandra chinensis* pollen extract (Cheng et al., 2019). The HSYA supplementation, a compound with a mono-chalcone glycoside structure, increased the abundance *of Akkermansia*, and the production of acetate, propionate, and butyrate. Moreover, the number of goblet cells and the expression of tight junction proteins ZO-1 were increased after intragastric supplementation with HSYA (Liu et al., 2018). Regarding the *S. chinensis* pollen extract, the most abundant phenolic compound was naringenin (1.89 mg/g), a flavanone. Treatment with pollen extract increased *Lactobacillus* in obese mice with a dose-effect relationship (Cheng, Chen, Liu, et al., 2019).

3.2.1.2. Other polyphenols. Prebiotic effect of other phenolic compounds, like lignans, phenolic acids, stilbenes and vanillin, was evaluated in five animal studies (Cho et al., 2016; Etxeberria et al., 2017; Guo et al., 2018; Qiao et al., 2014; Xie et al., 2019). In summary, there was an increase in the abundance of *Lactobacillus*, *Bifidobacterium* and *Akkermansia*, and a reduction in serum concentrations of pro-inflammatory cytokines and expression of lipid synthesis related genes.

The consumption of syringaresinol, a lignan present in oilseeds, cereal brans and berry seeds, enhanced the population of *Lactobacillus* and *Bifidobacterium*, and reduced serum lipopolysaccharide-binding protein (LBP) concentration (Cho et al., 2016). Supplementation with aqueous kudingcha extract, composed by 3,4-di-*O*-caffeoylquinic acids (3,4-diCQAs − 26.9%), 3,5-diCQAs (42.3%) and 4,5-diCQAs (30.8%), increased the abundance of *Bifidobacterium* and *Akkermansia*, and decreased the concentrations of serum interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α) and lipopolysaccharides (LPS) and the hepatic expression of lipid synthesis related genes (Xie et al., 2019). The supplementation with resveratrol, the largest representative of the stilbenes class, increased the abundance of *Lactobacillus* and *Bifidobacterium*, and decreased the genes expression related to fatty acids synthesis, adipogenesis and lipogenesis in mice fed a high-fat diet (Qiao et al., 2014). Animals treated with a standard diet supplemented with pterostilbene, a dimethoxy resveratrol derivative, showed an increase in the abundance of *Akkermansia muciniphila*, and an improvement in insulin sensitivity (Etxeberria et al., 2017). An increase in the production of acetate, propionate and butyrate and a decrease in the high concentrations of inflammatory factors (LPS, IL-6, and TNF-α) were observed in mice fed a high-fat diet after the supplementation with vanillin (Guo, Han, et al., 2018).

3.2.2. Clinical trials

The effect of anthocyanins was also evaluated in a crossover clinical trial, in which the consumption of a wild blueberry drink (375 mg of anthocyanins) by healthy adults increased *Bifidobacterium* spp. and *Lactobacillus acidophilus* (Vendrame et al., 2011). In another clinical trial with overweight-obese individuals, the consumption of pomegranate extract (1.8 g/day, 656 mg of phenolics) rich in hydroxybenzoic acids (punicalagins and free ellagic acid) increased *Faecalibacterium* and decreased the concentration of plasma LBP (González-Sarrías et al., 2018).

3.3. Methodological quality assessment of studies

The animal studies were generally classified as low or unclear regarding the risk of bias (Table S1). None of the included studies satisfied all areas established by the SYRCLE's tool for methodological quality assessment of animal studies. Data on selection bias (baseline characteristics and allocation concealment), performance bias (random housing and blinding), and detection bias (random outcome assessment and blinding) were unavailable in all studies. The clinical trials (González-Sarrías et al., 2018; Vendrame et al., 2011), evaluated by Cochrane Collaboration's tool, were at low-risk for selection bias (random sequence generation), performance bias (blinding of participants and personnel), reporting bias (selective reporting), and other bias. In addition, these studies were unclear for selection bias (allocation concealment) and detection bias (blinding of outcome assessment) and showed high-risk for attrition bias (incomplete outcome data).

4. Discussion

To our knowledge, this is the first systematic review aiming to explore the prebiotic effect of dietary polyphenols investigated in preclinical and clinical studies. We found 24 studies of which: 8 showed an increased abundance of *Lactobacillus* spp. and/or *Bifidobacterium* spp. (Cheng, Chen, Liu, et al., 2019; Cho et al., 2016; Dey et al., 2019; Li, Wu, et al., 2019; Ma et al., 2019; Qiao et al., 2014; Vendrame et al., 2011; Xie et al., 2019); 10 showed an increased abundance of *Akkermansia* spp. (Anhê et al., 2015, 2017; Dey et al., 2019; Etxeberria et al., 2017; Liu et al., 2018; Lu et al., 2019; Ma et al., 2019; Masumoto et al., 2016; Xia et al., 2019; Xie et al., 2019); 3 showed an increased abundance of *Faecalibacterium* spp. (González-Sarrías et al., 2018; López et al., 2018; Luo et al., 2019); and 3 showed an increased abundance of *Roseburia* spp. (Lu et al., 2019; Ma et al., 2019; Van Hul et al., 2018). Seven studies reported an increase in the production of SCFA, including butyrate (Guo, Han, et al., 2018; Henning et al., 2018; Li, Wu, et al., 2019; Liu et al., 2018, 2019; Luo et al., 2019; Wang et al., 2018).

The current definition of prebiotic recognizes that prebiotic targets extend beyond the stimulation of *Bifidobacterium* and *Lactobacillus*, and include other microorganisms such as *Roseburia*, *Eubacterium* and *Faecalibacterium* spp., but are not limited to these (Gibson et al., 2017). Thereby, the inclusion criteria applied in this systematic review is in accordance with the current concept of prebiotics. The health benefits associated with prebiotics are immune modulation, increased mineral absorption, improved bowel function, and a positive effect on glucose homeostasis, inflammation, blood lipid profile, satiety and defense against pathogens (Sanders et al., 2019). Although these effects cannot be easily extrapolated to the human gut microbiota, many of them seem to be mediated by SCFA, especially acetate, propionate, and butyrate.

The pathway that explains how polyphenols increase the production of SCFA is not yet fully understood. It is believed that the increase of anaerobic microorganisms, such as *Lactobacillus*, *Lachnospiraceae* and *Ruminococcaceae* can promote the increase of SCFA, especially of butyrate (Li, Wu, et al., 2019; Liu et al., 2018, 2019). Another possible explanation is associated with decafeinated green tea and black tea polyphenols that have been shown to inhibit α-amylase and α-glucosidase in saliva and small intestine, which may lead to residual carbohydrate in the large intestine providing substrate for the SCFA production (Henning et al., 2018). It is worth mentioning that SCFA are the major mediators among nutrition, gut microbiota, physiology, and pathology (Ríos-Covián et al., 2016). The butyrate has been investigated most extensively, and it is recognized that butyrate-producing bacteria and butyrate per se may be beneficial for human health (Koh, De Vadder, Kovatcheva-Datchary, & Bäckhed, 2016), suggesting it as a biomarker of prebiotic effect.

The studies reviewed here reported that the health benefits associated with the consumption of catechins were reduced concentrations of serum low-density lipoprotein cholesterol (LDL-c) (Ma et al., 2019), glucose and insulin (Wang et al., 2018). Studies also found that catechins could prevent an increase in toll-like receptor 4 (TLR4)/ nuclear factor kappa B (NFκB)-dependent inflammatory genes (Dey et al., 2019), and increase the hepatic adenosine monophosphate-activated

protein kinase (AMPK) phosphorylation (Henning et al., 2018). Besides, the consumption of green tea extract containing 48% epigallocatechin gallate prevented from a decrease in the expression of intestinal tight junction proteins induced by a high-fat diet (Dey et al., 2019). The treatment with soy isoflavone and HSYA improved intestinal barrier function through increasing the number of goblet cells and the expression of tight junction proteins ZO-1, occludin and Muc-2 (Liu et al., 2018; Luo et al., 2019). Digestive enzymes activities (β-glucosidase, β-galactosidase and β-glucuronidase) in the cecal environment were increased by the supplementation with anthocyanins (Li, Wu, et al., 2019). The health effects of proanthocyanidins consumption were improved glucose tolerance and insulin sensitivity, upregulation of lipid catabolism genes (PPARα), and downregulation of pro-inflammatory genes (COX2, TNFα) in the liver (Anhê et al., 2015, 2017; Masumoto et al., 2016).

Dietary flavonoids are consumed predominantly as glycosides (conjugated to sugar), which hinders the absorption of these compounds by the small intestine (Kawabata, Yoshioka, & Terao, 2019). Glycosylated flavonoids can serve as the sole source of carbon and energy for some microorganisms in the gut microbiota, which preferentially ferment the sugars linked to flavonoids. Thus, it could explain the prebiotic effect observed for these compounds (Braune & Blaut, 2016). For instance, aqueous extract of jaboticaba, a Brazilian native fruit rich in cyanidin-3-O-glucoside and delphinidin-3-O-glucoside, modulated the abundance of *Lactobacillus* and *Bifidobacterium* in rats with induced-colitis (Silva-Maia et al., 2019). Cyanidin-3-O-glucoside ameliorated gut microbial dysbiosis caused by 3-chloro-1,2-propanediol (chemical food contaminant) in rats (Chen et al., 2019). In other study, the Quzhou Fructus Aurantii extract, rich in naringin, a natural flavanone glycoside, increased the genus *Akkermansia* and the expression of tight junction proteins, and reduced metabolic endotoxemia in mice fed high-fat diet (Bai et al., 2019).

Most dietary polyphenols arrive intact in the colon, where they become substrates for the gut microbiota, producing better-absorbing metabolites (Mojzer et al., 2016; Kawabata et al., 2019). The flavonoids, such as epicatechin, catechin, procyanidin and quercetin, when metabolized by gut microbiota, generate hydroxy phenylacetic and hydroxyphenyl propionic acids (Shortt et al., 2018). Equol and O-desmethylangolensin (ODMA) are active metabolites produced by the action of colonic bacteria on soy isoflavones (Mayo, Vázquez, & Flórez, 2019). The urolithins, in turn, are metabolites produced from ellagitannins and ellagic acid by the human gut microbiota (Tomás-Barberán et al., 2017). These metabolites also have beneficial health effects, such as estrogenic and antioxidant activity (Mayo et al., 2019), anti-inflammatory and antioxidant effects (Lee, Park, Lee, Ahn, & Kim, 2019), and hepatoprotective effect (Zhao et al., 2018). Thus, further studies are warranted to investigate the potential of these metabolites as prebiotic effect markers, such as the SCFA modulation.

Studies with syringaresinol in male C57BL/6 mice (Cho et al., 2016) and pomegranate extract in overweight-obese individuals (González-Sarrías et al., 2018) demonstrated a decrease in serum LBP, indicating that polyphenols could modulate metabolic endotoxemia (Fuke, Nagata, Suganuma, & Ota, 2019). LBP is a glycoprotein mainly synthesized in the hepatocytes with long half-life in the blood and can bind to LPS promoting an LPS-induced immune response via toll-like receptors in macrophages (Jamar, Ribeiro, & Pisani, 2020). LPS, known as endotoxin, is a breakdown product present in the outer membrane of gram-negative bacteria, composed by an O-antigen portion in its outer part and by a lipid-A portion in its inner part. The lipid-A portion exerts most of the immunogenic effects, such as the activation of TLR4, through the formation of the complex containing LBP and the CD14 co-receptor, which signals the NFκB activation to upregulate pro-inflammatory mediators causing low-grade inflammation. The O-antigen portion activates components of the adaptive immunity, intending to induce the production of antibodies. Therefore, plasma LBP may be an inflammation marker caused by endotoxins (Jamar et al., 2020).

The dysbiosis of the gut microbiota caused by a high-fat diet has been considered as a possible cause for metabolic endotoxemia (Fuke et al., 2019). Thus, it is expected that the consumption of polyphenols may also improve the metabolic endotoxemia associated to dysbiosis, since the consumption of catechins (Liu et al., 2019; Lu et al., 2019), isoflavones (López et al., 2018; Luo et al., 2019), proanthocyanidins (Anhê et al., 2015; Masumoto et al., 2016), and dicaffeoylquinic acids (Xie et al., 2019) decreased plasma or serum LPS in animals fed a high-fat diet. Circulating LPS is released by lysis of a fraction of the bacterial cell wall and flows into the blood by increasing intestinal permeability. The excess intestinal LPS itself, caused by dysbiosis, destroys the narrow junction of intestinal epithelial cells via TLR4 and inhibits mRNA expression of factors related to the restricted junction, such as ZO-1 and occludin, in the intestinal epithelial cell. Therefore, LPS is considered an inflammation marker for dysbiosis (Fuke et al., 2019).

The improvement of the intestinal barrier function through increasing the expressions of ZO-1, occludin and Muc-2 genes, and of the mucin-producing goblet cells number is one of the possible mechanisms associated with the prebiotic effects of catechins (Dey et al., 2019), soy isoflavones (Luo et al., 2019) and HSYA (Liu et al., 2019). Kruppel-like factor 4 (KLF4), a marker of goblet cells, and Muc2 mRNA expression in the proximal colon were also associated with the administration of proanthocyanidins rich-cranberry extract, supporting that these polyphenols could be able to stimulate mucus production (Fig. 2), and therefore create an ecological niche for the *Akkermansia* spp., a mucus-degrading bacterium (Anhê et al., 2015). Xia et al. (2019) reported an increased abundance of *Akkermansia* spp. through an increase in other markers, such as type II and III secretion system proteins, the elongation factor thermo unstable, and a glyceraldehyde-3-phosphate dehydrogenase. This methodology was not observed in other studies. In this review, *Akkermansia* spp. was included as prebiotic target along with the bacteria recognized as probiotics by the Consensus Statement on the Definition and Scope of Prebiotics (Gibson et al., 2017), considering the recent evidences in literature about the relationship among *Akkermansia* spp., gut microbiota and human health (Cani & de Vos, 2017; Jayachandran, Chung, & Xu, 2019; Sanders et al., 2019). *Akkermansia* spp. and *Propionibacterium* spp. are promising candidates among the next generation of microorganisms to be recognized as prebiotic targets (Sanders et al., 2019).

There is also evidence of an additional mechanism by which polyphenols protect the intestinal barrier against oxidative stress. A decrease in the oxidative stress in the liver and ileum was observed in specific pathogen-free mice after a lower-dose consumption of green tea polyphenols (100 mg/kg body weight/day). The improvement of intestinal oxidative stress is supposed to be a potential mechanism for the modulation of tea polyphenols in the gut microbiota (Ma et al., 2019), since excess reactive oxygen species will damage the cell membrane and disrupt the tight junctions leading to an increased intestinal permeability and the development of metabolic disorders (Qiao, Sun, Ding, Le, & Shi, 2013). The tight junctions are multiprotein complexes that maintain barrier function between the enterocytes, creating paracellular barrier properties, which are composed by transmembrane proteins which control the transport across the intercellular space between adjacent cells and cytoplasmic plaque (Costea et al., 2019). The main components of the cytoplasmic plaque are claudin and zonula occludens proteins. In oxidative stress, the interactions of occludin with claudins or proteins of the zonula family are affected directly influencing the formation and function of the tight junctions. Oxidative stress downregulates occludin, reduces its specific membrane localization and regulatory contribution to barrier tightness via multiple signaling pathways (Costea et al., 2019). Nonetheless, most of the evidence is based *in vitro* and animal studies, and then further studies in humans are needed to clarify these mechanisms.

Regarding the methodological quality of the included papers, none of the studies satisfied all criteria established by the SYRCLE and Cochrane Collaboration's tool. No preclinical studies provide detailed descriptions of the methods used for allocation concealment, random

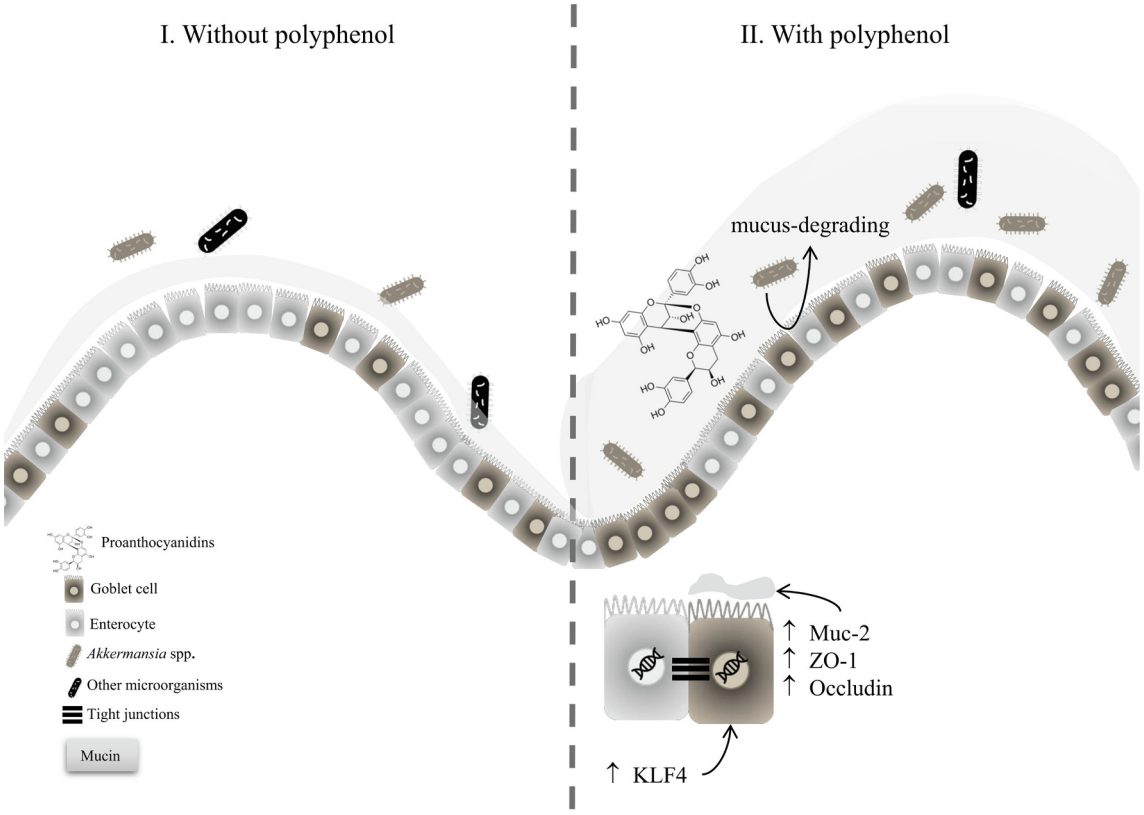

Fig. 2. Mechanism of mucin synthesis modulation by proanthocyanidins in the hindgut. KLF4: kruppel-like factor 4, Muc-2: mucin 2, ZO-1: zonula occludens 1. The consumption of polyphenols, represented in the figure by proanthocyanidins, may increase the number of goblet cells, according to the Kruppel-like factor 4 (KLF4) marker, and consequently, the mucin production; so the enhanced mucin provides a favorable environment for the proliferation of *Akkermansia* spp., a mucus-degrading bacterium (Anhê et al., 2015; Xia et al., 2019). In addition, increased expression of ZO-1 and occludin can be observed after the consumption of polyphenols, decreasing the intestinal permeability through the junction of epithelial cells (tight junctions) (Dey et al., 2019; Luo et al., 2019; Liu et al., 2019).

housing and random outcome assessment, or blinding researchers and outcome assessors. The clinical trials did not provide details on allocation concealment and blinding of outcome assessment. The absence of descriptions regarding sample losses in the preclinical and clinical studies also was noted. Therefore, we suggest the use of these tools in experimental planning, as a reference for well-designed studies aiming to reduce the risk of bias and allow more consistent conclusions.

It is noteworthy that the included studies had quite heterogeneous designs, including differences in the intervention period, the methodology for gut microbiome analysis, and the supplementation with polyphenol (food sample and dosage), as well as the polyphenols profile of the samples. Additional studies with isolated polyphenols are needed to eliminate the effects of other compounds in the extract, especially in clinical trials. Moreover, we suggest that further studies aiming to evaluate the prebiotic effect of dietary polyphenols should be carried out according to the internationally accepted prebiotics definition, with complete assessment of the gut microbiota, including the microorganism's genera. The low number of studies on humans is also a limitation in this systematic review.

5. Conclusion

The prebiotic effect of dietary polyphenols, especially catechins, anthocyanins, and proanthocyanidins, has strong evidence based on preclinical studies. Despite the limitations of these studies, it is evident that polyphenols can stimulate the growth of microorganisms recognized as prebiotic targets (*Lactobacillus* spp., *Bifidobacterium* spp., *Akkermansia* spp., *Roseburia* spp., and *Faecalibacterium* spp.), and increase the production of SCFA, including butyrate. Nevertheless, well-designed clinical trials are warranted to prove the prebiotic effect of polyphenols on humans.

Ethics statement

This research did not include any human subjects and animal experiments.

CRediT authorship contribution statement

Aline Medeiros Alves-Santos: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing - original draft, Writing - review & editing. **Clara Sandra Araújo Sugizaki:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing - original draft, Writing - review & editing. **Glaucia Carielo Lima:** Conceptualization, Data curation, Supervision, Visualization, Writing - review & editing. **Maria Margareth Veloso Naves:** Conceptualization, Data curation, Supervision, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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