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Review

Effects of Polyphenols in Tea (*Camellia sinensis* sp.) on the Modulation of Gut Microbiota in Human Trials and Animal Studies

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Abstract: A diet high in polyphenols is associated with a diversified gut microbiome. Tea is the second most consumed beverage in the world, after water. The health benefits of tea might be attributed to the presence of polyphenol compounds such as flavonoids (e.g., catechins and epicatechins), theaflavins, and tannins. Although many studies have been conducted on tea, little is known of its effects on the trillions of gut microbiota. Hence, this review aimed to systematically study the effect of tea polyphenols on the stimulation or suppression of gut microbiota in humans and animals. It was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. Articles were retrieved from PubMed and Scopus databases, and data were extracted from 6 human trials and 15 animal studies. Overall, large variations were observed in terms of microbiota composition between humans and animals. A more consistent pattern of diversified microbiota was observed in animal studies. Tea alleviated the gut microbiota imbalance caused by high-fat diet-induced obesity, diabetes, and ultraviolet-induced damage. The overall changes in microbiota composition measured by beta diversity analysis showed that tea had shifted the microbiota from the pattern seen in animals that received tea-free intervention. In humans, a prebiotic-like effect was observed toward the gut microbiota, but these results appeared in lower-quality studies. The beta diversity in human microbiota remains intact despite tea intervention; supplementation with different teas affects different types of bacterial taxa in the gut. These studies suggest that tea polyphenols may have a prebiotic effect in disease-induced animals and in a limited number of human interventions. Further intervention is needed to identify the mechanisms of action underlying the effects of tea on gut microbiota.

Keywords: *Camellia sinensis*; tea polyphenols; gut microbiota; gastrointestinal bacteria; systematic review

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1. Introduction

Studies on the relationship between gut microbiota and health have garnered much interest in recent years. The term "gut microbiota" is defined as the microbial ecosystem or community that resides within the human intestinal tract [1]. The gut ecosystem comprises microorganisms, mainly bacteria, and a small number of viruses, protozoa, and eukaryotic organisms such as fungi that are distributed throughout the gastrointestinal tract [2]. As stated by Nahoum et al., 2016, diversified microbiota are a crucial indicator of good health and well-being [3].

Gut microbiota play an important role in human health, and they are considered a "forgotten organ" and "super-organism" that maintains intestinal epithelium integrity [4–6]. The human gut contains an estimated 100 trillion microorganisms [7]; in addition, over 1000 different species of microbes colonize the human gut [8]. The dominant groups of bacteria phyla in the gut are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* [5,9]. *Fusobacteria*, *Cyanobacteria*, and *Verrucomicrobia* phyla are usually less well-represented [10].

Gut microbiota may also play a role in how drugs are metabolized in our body [11]. These commensal bacteria play important roles as key regulators of digestion, involving the extraction, synthesis, and absorption of many nutrients and metabolites, including bile acids, lipids, amino acids, vitamins, and short-chain fatty acids (SCFAs) [11]. The gut microbiota also have a crucial immune function against pathogenic bacteria colonization through many competition processes [12]. They inhibit pathogenic bacteria growth by consuming available nutrients, by pH modification, and by producing bacteriocins, which are a type of antimicrobial peptide secretion, affecting cell signaling pathways [13].

Gut microbiota imbalance (dysbiosis) is associated with the development of a series of diseases [14–19]. These diseases include diabetes, obesity, cardiovascular and liver diseases, cancers, multiple sclerosis, and neurodegenerative diseases [14–19]. Hence, the gut microbiota has been proposed as a promising therapeutic target for these diseases [20].

Research is still ongoing into the factors that modulate gut microbiota profiles, and diet could play a role [21–23]. However, studies suggest that diet only accounts for a low percentage of microbiome variation after adjusting for other contributing co-variates, such as genetics, age, ethnicity, geographic origins, body mass index (BMI), lifestyle, medication, and environmental factors [12,24].

Dietary intake varies from one individual to another, and there is a complex interaction between dietary intake and the gut microbiome [25]. The so-called "Western diet" is characterized as high-calorie and is associated with metabolic syndrome i.e., abnormal lipid profiles, elevated blood pressure, and impaired fasting glucose [2]. Evidence suggests that the so-called "Mediterranean diet," which is high in the polyunsaturated fatty acids and polyphenols (from coffee, tea, or grapes), is associated with an increased gut microbiota diversity [26].

Tea (*Camellia sinensis* sp.) is one of the most widely consumed nonalcoholic beverages in the world [27]. There are different types of tea: green tea, oolong tea, black tea, Pu-erh tea, and dark tea. Each tea is produced differently using different fermentation processes. Tea is rich in polyphenols, possesses antioxidant properties, and offers multiple health benefits [28]. Flavonoids such as flavanols (catechins, gallocatechins, and epicatechins), flavonols (kaempferol and quercetin), and phenolic acids are the three major classes of polyphenols in tea [29].

Polyphenols are absorbed in the small intestine and may reach the colon [30]. These polyphenols may modulate the gut microbiota composition, and the gut microbiota may catabolize polyphenols into metabolites such as phenolic acids [31]. The metabolites are absorbed more efficiently compared with the parent polyphenols compounds. These metabolites might be further conjugated as O-methylated, sulphated, and glucuronidated in the liver before being excreted [32]. In vitro studies have shown that the polyphenols in tea are biotransformed to active metabolites by the gut microbiota through enzymatic activities and the increased bioavailability of polyphenols [33,34]. Polyphenols such as flavanols, including catechins, modulate the composition of the gut microbial community, mostly through the inhibition of pathogenic bacteria and the stimulation of beneficial bacteria species such as *Bacteroides galacturonicus*, *Lactobacillus* sp., *Enterococcus caccae*, *Bifidobacterium catenulatum*, *Ruminococcus gauvreauii*, and *Escherichia coli* [34,35]. Previous studies have shown that the synergistic effect of tea polyphenols and gut microbiota has subsequently influenced the host biochemical processes, establishing a system of mutual interaction and inter-dependency [36]. The presence of polyphenols could increase the host immune system and metabolic responses through the modulation of gut microbiota [36].

Evidence suggests that polyphenols may also modulate the gut microbiota in what is known as a prebiotic-like effect [20]. However, Ivey et al., 2019 reported that dietary flavanols produce a vast potential complexity of interactions when combined with the phylogenetic and functional diversity of the human gut microbiota [37]. This complexity is linked to the capacity of flavanols to promote beneficial bacteria or suppress pathogenic bacteria [38–40].

To the best of our knowledge, the effects of tea on gut microbiota were studied in cells (in vitro) and in mechanistic studies on animal models (in vivo) [41–44]. However, studies using cell lines or animal models to study gut microbiota have their own limitations. Casotta et al., 2020 showed that findings from animal models and cell cultures do not represent and are not translatable to humans [45]. The main limitation of in vivo studies is due to the host's tolerance of microbial infections, which varies greatly across different species [46]. In vitro colonic fermentation models are cheaper, are more reproducible, and can be conducted in a shorter time compared with in vivo studies [47]. Pham et al., 2018 showed several limitations of cell studies, including the absence of human or animal cells and low pH, which reduces microbial activity [47].

Furthermore, it remains a challenge to translate findings obtained from cells and animal models to humans [48]. The role of polyphenols in tea in modulating the human gut microbiota is not well understood. This highlights the need and importance of standardizing human studies, and better outcomes could be predicted. It is still too unclear to suggest an effective dose, choice of types (green, oolong, black, or dark tea) or forms (liquid, powder, or extract), and the duration of tea intake needed to increase the diversity of the gut microbiota in humans. Therefore, this systematic review aimed to contribute to the current updated evidence and knowledge on tea polyphenol stimulation or suppression of the diversity in gut bacteria population in humans and animals. The next aim was to determine the effective types of tea (green, black, oolong, or dark tea), dosage, tea forms (liquid, powder, or pure extract), and duration of intake to modulate the gut microbiota.

2. Methods

2.1. Search Strategy

Studies were selected using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two search databases, namely PubMed and Scopus, were used to search for articles published between the years 2000 and 2020. The Boolean operator term AND was used to focus and narrow the search, while OR was used to expand the search by linking synonyms. The following key terms were applied during the search:

(Tea) AND (Gut Microbiota OR Gut Microbiome OR Gut Microflora):

1. (Tea Polyphenol OR Tea Catechin) and (Intestinal Microbiota OR Intestinal Flora)
2. (Caffeinated Tea OR Decaffeinated Tea) AND (Colon Microbiota OR Colon Microbial)
3. (Green Tea OR Black Tea OR Oolong Tea) AND (Gut Bacteria OR Enteric Bacteria)
4. (Tea OR *Camellia sinensis* sp.) AND (Gastrointestinal Microbiota OR Gastrointestinal Bacteria)
5. (Tea) AND (*Firmicutes* OR *Bacteroidetes* OR *Actinobacteria* OR Proteobacteria)
6. (Flavonoids OR Flavanols OR Flavonols OR Phenolic acids) AND (Gut Microbiota OR Gut Microbiome OR Gut Microflora
7. (Catechin OR Gallocatechin OR Gallocatechin gallate OR Epicatechin OR Epicatechin gallate OR Epigallocatechin OR Epigallocatechin gallate) AND (Gut Microbiota OR Gut Microbiome OR Gut Microflora)

2.2. Study Selection

Two authors independently screened the articles and extracted the data. Jadad scoring was used to assess the risk of bias in human trials. The lowest possible score is 1, while the highest possible score is 5 (indicating the highest-quality human trials) [49]. Studies were qualified for eligibility according to pre-specified inclusion criteria. The inclusion criteria were: (1) English primary research paper published between 2000 and 2020; (2) papers on randomized control trials and in vivo studies; (3) studies with normal or overweight (BMI of 18.5–29.9) subjects, non-smokers and non-drinkers, free from medications or supplements; (4) subjects who have had a low-polyphenol diet before enrolling into intervention; (5) all subjects given *Camellia sinensis* tea and compared with placebo and/or no treatment;

(6) study outcomes measuring gut microbiota diversity, including alpha diversity (richness, evenness, and relative abundance) and beta diversity (overall bacteria composition).

3. Results

A total of 5671 articles on human trials and in vivo animal studies were retrieved from the preliminary search using Scopus and PubMed. Duplicate articles (n = 2663) were removed and the remaining 3008 articles were screened for the relevant title and abstract. A total of 2963 nonrelevant articles were further excluded, and the remaining 45 articles were screened for full content. Twenty-four articles did not meet the inclusion criteria and were excluded. Among those, fifteen studies were excluded because they used multi-component tea supplements in the intervention. Eight studies focused on urinary metabolites of the gut microbiota rather than the composition of the commensal microorganism; thus, they were excluded. One randomized control trial described only intervention protocols and, hence, was excluded. A total of 6 human trials and 15 animal studies were included in the final qualitative review (n = 21); Figure 1 shows the PRIMA flow diagram. Three human studies showed a "high" risk of bias, as assessed by the Jadad score (Table 1).

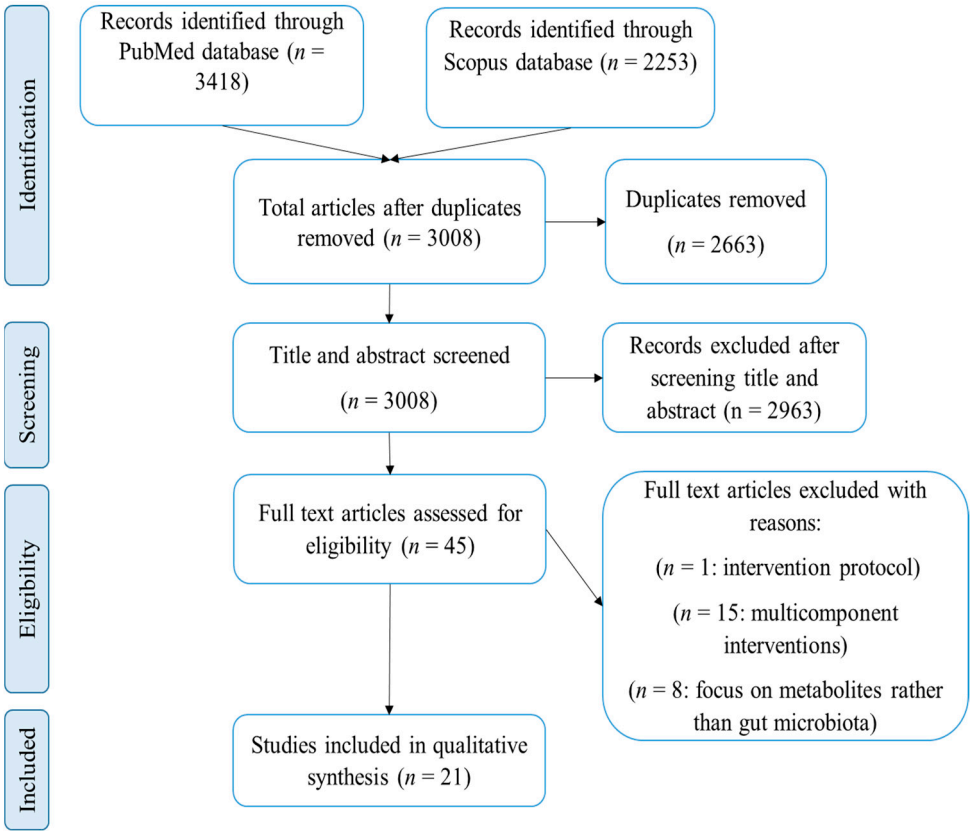

Figure 1. PRISMA flow diagram used to identify human trials and animal studies.

Table 1. Risk of bias assessment based on Jadad score.

Reference	Jaded Scores	Study Quality
Zhou et al., 2019 [50]	5	High
Mai et al., 2004 [51]	5	High
Janssens et al., 2016 [52]	4	High
Yuan et al., 2018 [53]	0	Low
Huang et al., 2019 [54]	0	Low
Jin et al., 2012 [55]	0	Low

3.1. Green Tea and Gut Microbiota

Green tea is processed swiftly using fresh leaves to prevent fermentation [28]. Thus, the polyphenol content is higher in green tea compared with other types of tea [28]. Tables 2 and 3 summarize the findings on four human trials and five animal studies on the modulation effects of green tea and the gut microbiota.

No changes were observed in the gut microbiota from a high-quality clinical trial administering four decaffeinated green tea capsules daily containing 1315 ± 115.0 mg of catechins in post-menopausal women for one year [50]. Another trial observed the same results, except for the fact that overweight subjects showed a lower microbiota diversity compared with normal-body-weight subjects before the intervention [52]. Yuan et al., 2018 found that tea reversed the gut microbiota patterns seen in patients with colorectal cancer [53,56–59]. However, it must be noted that Yuan et al., 2018 showed a low Jadad score for study quality [53]. The same study found increased levels of bacteria responsible for producing short-chain fatty acids (the main energy source of cells in gut lumen) after receiving 400 mL of green tea beverage per day (approximately two cups daily) for two weeks [53]. Jin et al., 2012 found an increase in probiotic *Bifidobacteria* when the subjects replaced their water with green tea liquids for ten days [55].

The effects of green tea in animal models were consistent. Mice were given different stressors to cause dysbiosis (imbalances) in their gut microbiota. Zhang et al., 2020 supplemented the diet of diabetic-induced mice with green tea for one month [60]. Diabetes had shifted all diversity measures of the microbiota, and incorporating tea in the diet lowered the indexes to levels almost similar to those in normal mice [60]. Wang et al., 2018 administered tea as drinking water along with a high-fat diet in human flora-associated mice for eight weeks [61]. Tea reversed all changes induced by obesity, hence increasing the overall microbial diversity [61]. Wang et al., 2016 supplemented green tea in a high-fat diet and showed an increased abundance of beneficial lactic acid bacteria (*Lactobacillus* sp.) [62]. Jung et al., 2017 exposed the mice to chronic ultraviolet rays, which subsequently changed the dominant phylum of microbiota [63]. Receiving tea extract for 10 weeks completely reversed the changes induced in the mice by the ultraviolet rays [63]. Seo et al., 2015 found a significant reduction in biomarkers of obesity and insulin resistance (ratio of *Firmicutes* to *Bacteroidetes* phyla and ratio of *Bacteroidetes* to *Prevotella* phyla) in the high-fat diet group after intubating tea extracts orally for eight weeks [64].

Table 2. Modulatory effects of tea in human studies (n = 6).

Reference	Subjects	Dose, Duration	Alpha Diversity			Beta Diversity	Key Findings
			Richness	Richness, Evenness	Relative Abundance		
Zhou et al., 2019 [50] Country: United States	124 post-menopausal females	Four green tea pills/day (1315 ± 115.0 mg catechins) for 12 months	No change	No change	No changes in *Firmicutes*, *Bacteroidetes*, or *Actinobacteria*	No change	Green tea does not affect gut microbiota
Yuan et al., 2018 [53] Country: China *	12 healthy normal and overweight males and females	400 mL/day (100.2 µg GAE/mL of total polyphenols) for 2 weeks	Increased	Increased	↓*Bacteroidetes*, ↑*Firmicutes*, ↑*Actinobacteria* ↑FIR:BAC, ↑*Lachinospiraceae*, ↑*Ruminococcaceae*, ↑*Dorea*, ↑*Roseburia*, ↑*Feacalibacterium*, ↑*Eubacterium*, ↑*Blautia*, and ↑*Coprococcus*	Changed	Green tea significantly increased microbial diversity
Janssens et al., 2016 [52] Country: United States	58 Caucasian normal to overweight males and females	Nine green tea pills/day (0.56 g of EGCG) for 12 weeks	Not measured	No change	No changes in *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Fusobacteria*, or *Verrucomicrobia*	No change	Green tea does not affect gut microbiota
Jin et al., 2012 [55] Country: Japan *	10 nonhabitual male and female tea drinkers	1000 mL green tea/day (unknown amount of polyphenols) for 10 days	Not measured	Not measured	↑*Bifidobacteria*	Not measured	Green tea increased probiotic *Bifidobacteria*
Mai et al., 2004 [51] Country: United States	8 hypercholesterolemia subjects	Black tea infusion (unknown dose and polyphenol amount) for 6 weeks	Not measured	Not measured	No changes in *Bacteroides*, *Prevotella Faecalibacterium*, *Bifidobacteria*, *Atopobium*, *Clostridium*, or *Ruminococci.* ↓Unknown species	Not measured	Black tea does not affect gut microbiota
Huang et al., 2019 [54] Country: China *	13 normal and overweight males	50 mg/kg/day of instant Pu-erh tea infusion (52.75% theabrownin) for 4 weeks	Not measured	Not measured	↓*Bacilli*, ↓*Clostridia*, ↓*Lactobacillus*, ↓*Bacillus*, ↓*Streptococcus*, and ↓*Lactococcus*	Changed	Pu-erh tea reduced diversity of hyper-cholesterol-enriching bacteria

FIR:BAC = ratio of *Firmicutes* to *Bacteroidetes* phyla; EGCG = Epigallocatechin-3-gallate. Asterisks (*) indicate a low-quality study based on Jadad Score (Table 1).

Table 3. Modulatory effects of tea in animal studies (n = 15).

Reference	Dose, Duration	Alpha Diversity			Beta Diversity	Key Findings
		Richness	Richness, Evenness	Relative Abundance		
Zhang et al., 2019 [60]	0.1 g of matcha powder (14% tea polyphenols and 4.5% EGCG) or instant green tea (22.7% tea polyphenols and 8.4% EGCG) per 100 g of diet for 30 days	Increased	Increased	↓*Firmicutes*, ↑*Bacteroidetes* ↑*Actinobacteria*, ↓*Proteobacteria*, ↑*Coriobacteriaceae*, ↑*Lactobacillaceae*, ↑*Bifidobacteriaceae*, ↑*Prevotellaceae*, ↓*Bacteroidaceae*, ↓*Ruminococcaceae*, ↓*Helicobacteraceae*, and ↓*Enterobacteriaceae*	Changed	Tea increased diversity of microbiota, reversing the changes caused by diabetes
Wang et al., 2018 [61]	0.05, 0.2, and 0.8 g of green tea extract per 100 mL of water (contains 804 mg/g of total catechins and 455 mg/g EGCG) in HFD for 8 weeks	Not measured	Increased	↓*Firmicutes*, ↑*Bacteroidetes*, ↓FIR:BAC, ↑*Bacteroides*, ↑*Turicibacter*, ↑*Lachnospira*, and ↓*Clostridium*	Changed	Tea increased diversity of microbiota, reversing the changes caused by obesity
Wang et al., 2016 [62]	0.05, 0.2, and 0.8 g of green tea polyphenol compound per 100 g of HFD for 8 weeks	Not measured	Increased	↑*Lactobacillus*	Changed	Tea increased beneficial *Lactobacillus*
Jung et al., 2017 [63]	1 g extract/100 g diet (contains 50% of total catechins) for 10 weeks	Not measured	Increased	↓*Firmicutes*, ↑*Bacteroidetes*, and ↑*Proteobacteria*	Not measured	Tea increased diversity of microbiota, reversing the changes caused by chronic ultraviolet exposure
Seo et al., 2015 [64]	500 mg of fermented green tea extract/kg in HFSD (contains 7.85% catechins) for 8 weeks	Not measured	Not measured	↓FIR:BAC and ↓BAC:PREV	Not measured	Tea reduced biomarkers of obesity and insulin resistance
Cheng et al., 2018 [43]	0.1 g of oolong tea polyphenols per 100 g of HFD (contains 43.55 ± 3.77 μg/g of EGCG) for 4 weeks	Not measured	Increased	↓*Firmicutes*, ↑*Bacteroidetes*, ↓FIR:BAC, and ↑*Proteobacteria*	Changed	Tea increased diversity of microbiota, reversing the changes caused by obesity
Cheng et al., 2017 [41]	0.1 g oolong tea polyphenols (EGCG) per 100 g of HFD for 8 weeks	Not measured	Increased	↓*Firmicutes*, ↑*Bacteroidetes*, ↓FIR:BAC, and ↑*Proteobacteria*	Changed	Tea increased the diversity of microbiota, reversing the changes caused by obesity
Huang et al., 2019 [54]	450 mg/kg/day of ripe Pu-erh tea extracts in HFD (containing 52.75% theabrownin) for 26 weeks	Not measured	Not measured	↓*Bacilli*, ↓*Lactobacillus*, ↓*Bacillus*, ↓*Enterococcus*, ↓*Lactococcus*, and ↓*Streptococcus*	Changed	Pu-erh tea reduced the diversity of hyper-cholesterol-enriching bacteria
Lu et al., 2019 [65]	0.1, 0.2, and 0.4 g of ripe Pu-erh tea extract per 100 mL of water in HFD (contains 4156.63 mg/kg of epicatechins) for 8 weeks	Increased	Increased	↓FIR:BAC, ↑*Anaerotruncus*, ↑*Alistipes*, ↑*Odoribacter*, ↑*Akkermansia*, ↑*Blautia*, ↑*Roseburia*, ↑*Bacteroides*, ↑*Parabacteroides*, ↓*Bilophila*, ↓*Leuconostoc*, and ↓*Allobaculum*	Changed	Tea increased the diversity of microbiota, reversing the changes caused by obesity

Table 3. *Cont.*

Reference	Dose, Duration	Alpha Diversity			Beta Diversity	Key Findings
		Richness	Richness, Evenness	Relative Abundance		
Xia et al., 2019 [66]	0.15 and 0.4 g extracts/kg body-weight of raw Pu-erh tea (2.73 ± 0.28% of catechin) and ripe Pu-erh tea (contains 0.56 ± 0.07% of catechin) in HFD for 5 weeks	Increased	Increased	↑*Firmicutes*, ↓*Bacteroidetes*, and ↑*Actinobacteria*	Not measured	Tea increased the diversity of microbiota, reversing the changes caused by obesity
Gao et al., 2017 [67]	750 mg/kg of ripe Pu-erh tea extract and 250 mg/kg of Pu-erh tea polyphenol and oxidized tea polyphenol in HFD for 12 weeks	Not measured	Not measured	↑*Firmicutes*, ↓*Bacteroidetes*, ↑FIR:BAC, ↑*Eubacterium rectale*, ↑*Clostridiumcoccoides*, ↑*Faecalibacterium prausnitzii*, ↑*Akkermansia muciniphila*, ↑*Bifidobacterium*, ↑*Lactobacillus*, and ↑*Roseburia*	Not measured	Tea increased the diversity of microbiota, reversing the changes caused by obesity
Chen et al., 2018 [42]	400 mg/kg/day of Fuzhuan tea extract (contains 26.05 ± 1.15% polyphenols) in HFD for 8 weeks	Not measured	Increased	↓*Firmicutes*. ↑*Bacteroidetes*, ↓FIR:BAC, ↑*Proteobacteria*, and ↑*Bifidobacteriaceae*	Changed	Tea increased the diversity of gut microbiota and beneficial bacteria, reversing the changes caused by obesity
Foster et al., 2016 [68]	1400 mg/kg/week of Fuzhuan tea extract (unknown polyphenol amount) in HFD for 8 weeks	Not measured	Not measured	↓*Firmicutes*, ↑*Bacteroidetes*, and ↑*Lactobacillus*	Not measured	Tea increased the diversity of gut microbiota, reversing the changes caused by obesity
Henning et al., 2017 [69]	0.5 g of decaffeinated green tea extract (contains 565 ± 24 GAE mg/g) or black tea extract (contains 532 ± 25 GAE mg/g) per 100 g of HFD for 4 weeks	Not measured	Not measured	↑*Bacteroidetes*, ↓*Firmicutes*, ↓*Actinobacteria*, ↓FIR:BAC, ↑*Parabacteroides*, ↑*Clostridium*, ↑*Coprococcus*, and ↑*Pseudobutyrivibrio*	Changed	Tea increased the diversity of gut microbiota, reversing the changes caused by obesity
Liu et al., 2016 [70]	100 mL tea infusion of green tea (contains 3332.35 ± 70.91 mg/L of total polyphenols), oolong tea (contains 2911.52 ± 51.51 mg/L of total polyphenols), and black tea (contains 2732.11 ± 23.64 mg/L total polyphenols) in HFD for 13 weeks	Increased	Increased	↑*Alistipes*, ↑*Rikenella*, ↑*Lachnospiraceae*, ↑*Akkermansia*, ↓*Bacteroides*, and ↓*Parabacteroides*	Changed	Tea increased the diversity of gut microbiota, reversing the changes caused by obesity

Total phenolic content is expressed as GAE; GAE = gallic acid equivalent; HFD = high-fat diet; EGCG = Epigallocatechin-3-gallate; HFSD = high-fat sugar diet; FIR: BAC = ratio of *Firmicutes* to *Bacteroidetes* phyla; BAC: PREV = ratio of *Bacteroidetes* to *Prevotella.*

3.2. Oolong Tea and Gut Microbiota

Oolong tea is also known as "semi-fermented" or "partially oxidized" tea. Catechins in oolong tea are oxidized into theaflavins, thearubigins, and theabrownins during partial fermentation, hence producing a slightly darker color than green tea [71]. Oolong tea was supplemented in two murine studies (Table 3). Studies by Cheng et al. investigated the effects of oolong tea extracts in mice induced with human flora and given a high-fat diet [41,43]. Tea increased gut microbiota diversity after four to eight weeks of tea supplementation [41,43].

3.3. Black Tea and Gut Microbiota

Black tea is a "fully fermented" tea and is characterized by a darker color and astringent taste due to a higher concentration of theaflavins, thearubigins, and theabrownins compared to other types of tea [71,72]. Polyphenol oxidase is a heat-labile enzyme present in black tea [72]. The activity of this enzyme is reduced by steam-heating during the fermentation of black tea, consequently reducing its antioxidant properties compared to green tea [72,73]. In this review, one human study demonstrated the effect of black tea on the gut microbiota (Table 3). Black tea infusion was given to hypocholesterolemic volunteers in a double-blind, randomized crossover feeding trial for six weeks [51]. However, no significant changes were observed in the gut microbiota [51].

3.4. Pu-erh Tea and Gut Microbiota

Pu-erh tea is a traditional Chinese tea. There are two types of Pu-erh tea, namely raw (unfermented) and ripe (after microbial fermentation) [74]. In this review, one human trial and four murine studies were done on Pu-erh tea (Tables 2 and 3). Huang et al., 2019 investigated the cholesterol-lowering activity of ripe Pu-erh tea in humans and animals [54]. In this study, male human subjects received 600 mL of tea infusion (approximately three cups) daily for four weeks, while the mice were provided with a daily dose of 450 mg of tea extracts per kg body weight in a high-fat diet for 26 weeks [54]. Hyper-cholesterol-enriching bacterial genera were significantly reduced compared to high-fat diet numbers in human and animal studies [54]. Three murine studies demonstrated the effects of raw and ripe Pu-erh tea in restoring the altered gut microbiota caused by a high-fat diet. Lu et al., 2019 and Xia et al., 2019 showed that Pu-erh tea at a dose between 0.1 to 0.4 g of tea extracts for five to eight weeks effectively increased gut microbiota diversity [65,66]. Gao et al., 2017 found that ripe Pu-erh tea extract and Pu-erh tea polyphenol components increased gut microbiota diversity in the high-fat diet group [75].

3.5. Fuzhuan Tea and Gut Microbiota

Fuzhuan brick tea is a type of dark tea known as fungal fermented tea [76]. The polyphenol content in Fuzhuan tea is lower compared to green tea, due to the process of microbial fermentation occurring in dark tea production [77,78]. A series of reactions, including degradation, oxidation, condensation, structural modification, methylation, and glycosylation, are catalyzed by microbial exo-enzymes or occur as a result of microbial metabolism, leading to the development of dark tea quality [79–81]. Studies by Chen et al., 2018 and Foster et al., 2016 incorporated two different dosages of Fuzhuan tea extracts in mice receiving a high-fat diet (Table 3) [42,68]. Daily supplementation of Fuzhuan tea extracts at doses of between 200 to 400 mg for eight weeks was able to reverse the altered dominant phyla bacteria in the gut and also increase the levels of *Lactobacillus* and *Bifidobacteriaceae* [42,68].

3.6. Multiple Types of Tea and Gut Mmicrobiota

Two murine studies compared the modulating effects of multiple teas on the gut microbiota that were exposed to a high-fat diet (Table 3) [69,70]. Henning et al., 2017 showed that the supplementation of 0.5 g of decaffeinated green and black tea extract daily for four weeks increased the level of phylum *Bacteroidetes* while suppressing phyla *Firmicutes*

and *Actinobacteria* [69]. The ratio of *Firmicutes* to *Bacteroidetes* was also reduced [69]. Liu et al., 2016 monitored the effects after feeding 100 mL of either green, oolong, or black tea liquid daily for 13 weeks, and they noted a reversed trend in the growth of bacteria, compared to those with only a high-fat diet [70].

4. Discussion

Gut microbiota are known for their large variations in terms of taxonomy and functionality [12]. Each individual has a unique gut microbiota profile that differs from another's [12]. Genetic and environmental factors directly influence gut microbiota composition [81]. In terms of genetics, the gut microbiota can be shaped according to birth gestational age, type of birth delivery, methods of milk-feeding, and weaning period [12]. The composition of gut microbiota also differs greatly due to many lifestyle-associated factors, including dietary choices, physical activity, body mass index (BMI), age, food additives and contaminants, and antibiotic consumption, which indirectly shape the gut microbiota composition [24,82].

This review showed that *Camellia sinensis* could modulate the gut microbiota. Overall, 3 human studies and 15 animal studies from a total of 21 included in the review showed a significant increase in diversity of the gut microbiota. Most animal studies were able to reverse the disrupted microbiota changes due to stressors such as diabetes, obesity, and ultraviolet ray damage. The beta diversity measured in murine studies showed an overall shift in the mice gut microbiota profile after tea supplementation. This indicates that the modulatory effects of tea were attributable to its ability in mediating specific imbalances in the gut. Three out of six human trials showed diversified microbiota as a result of incorporating tea [53–55]. An increase in the richness, evenness, and relative abundance of beneficial bacteria and a reduction in nonbeneficial bacteria were observed in the studies [53–55].

Green tea was the main type of tea used in this review. An average of two to five cups of green tea per day for 10 days and up to two weeks was associated with increased beneficial probiotic *Bifidobacteria* and their colon cancer-preventative properties in humans [53,55]. Colonic microbiota have the ability to metabolize tea polyphenols into short-chain fatty acids (SCFA) and phenolic acids, before being metabolized in the liver or being excreted [83]. A previous in vitro study showed that black tea prepared in bread had no impact on short-chain fatty acid (SCFA) production [84]. One portion of the bread containing 30% of polyphenols could be obtained from a cup of black tea [84].

In a low-quality human trial, green tea increased clusters of bacteria specializing in producing short-chain fatty acids (SCFA), namely *Lachinospiraceae*, *Ruminococcaceae*, *Dorea*, *Roseburia*, *Feacalibacterium*, *Eubacterium*, *Blautia*, and *Coprococcus* [53]. Short-chain fatty acids are a primary energy source for colonic epithelium cells, as they maintain intestinal homeostasis through anti-inflammatory actions [85,86]. With elevated fecal SCFA concentrations, SCFA-producing bacteria may promote reduced inflammation in the gut [85,86]. This might be important in the preventative steps against colorectal cancer, as inflammatory bowel disease patients showed reduced levels of dominant SCFAs-producing bacteria in several studies [87–91]. However, further study is needed to determine whether green tea could possibly modulate the gut microbiota in cancer patients.

Daily Pu-erh tea intakes of 600 mL (around three cups) for four weeks reduced the proliferation of hypercholesterol-enriching bacteria (*Bacilli*, *Clostridia*, *Lactobacillus*, *Bacillus*, *Streptococcus*, and *Lactococcus*) [54]. These bacteria are involved in bile acid metabolism, i.e., to generate bile salt hydrolase (BSH) enzymes that reduce cholesterol level [54]. Obese human subjects showed a higher *Firmicutes*/*Bacteroidetes* ratio after supplementation with polyphenols, and this has been proposed as a reason for weight loss [92,93]. A previous study showed that body weight and dramatic dietary patterns might affect the gut microbiota composition [94,95]. There was no substantial difference in bacterial composition after green tea supplementation in normal human subjects, and this could be due to

their "optimum" state of energy balance [52]. However, more human trials are needed to confirm this.

Previous studies have shown that obese animals and humans have higher *Firmicutes*/*Bacteroidetes* ratios and higher *Firmicutes* compared with normal-weight individuals, proposing this ratio as a potential biomarker of obesity [96–100]. However, few studies have proved that a high-fat diet decreased both bacteria levels [67,68]. Tea supplementation increased the *Firmicutes*: *Bacteroidetes* ratio and *Firmicutes* compared with the high-fat group alone [67,68]. A recent human trial showed a higher *Firmicutes*:*Bacteroidetes* ratio and higher *Firmicutes* in normal-weight subjects after tea supplementation [53].

Meta-analyses failed to observe a clear correlation between the ratios of these two phyla and obesity, suggesting the complexity of how the gut microbiome modulates obesity [101]. Although the gut microbiota could contribute to the development of obesity, the evidence suggesting an association between obesity and alterations of the *Firmicutes*: *Bacteroidetes* ratio and *Firmicutes* is not convincing [82]. Thus, tea certainly has effects on the relative species abundance of the gut microbiota, although interpretations of the findings are still lacking [43].

In general, this review showed that low doses of tea might increase the gut microbiota diversity in a short period of time, compared with higher tea doses given for a longer period. A longer period of consumption with higher doses diminished the effects observed during a short period of supplementation. This suggests that the human gut microbiota are resilient toward longer and higher doses of tea supplementation. Human microbiota are stable upon reaching adulthood, and the composition of the gut microbiota remains relatively unaffected by acute perturbations, as its plasticity-like characteristics allow it to return rapidly to its initial composition [102,103]. This review showed a high variability in terms of different types of tea, food matrix, doses, and duration of tea supplementation. Each study used a different type of approach, i.e., richness, evenness, relative abundance, and β diversity.

5. Conclusions

Tea could increase alpha and beta diversities of the gut microbiota in animals, regardless of tea type, forms, dosage, and duration of intake. However, few effects were observed in humans due to a higher inter-variation in gut microorganisms between individuals. However, the exact mechanism of how tea affects trillions of microbiota in the gut is still poorly understood. More vigorous studies and trials on tea and gut microbiota are needed to understand the effects. While new evidence is needed, *Camellia sinensis* should be considered as a source of polyphenols in the diet. However, given the differences within and between human and animal studies, there is no specific dose and duration of tea that could be recommended for a healthy gut microbiota.

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References

1. Kumar Singh, A.; Cabral, C.; Kumar, R.; Ganguly, R.; Kumar Rana, H.; Gupta, A.; Rosaria Lauro, M.; Carbone, C.; Reis, F.; Pandey, A.K. Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. *Nutrients* **2019**, *11*, 2216. [CrossRef]
2. Cresci, G.A.; Bawden, E. Gut Microbiome: What We Do and Don't Know: What We Do and Don't Know. *Nutr. Clin. Pract.* **2015**, *30*, 734–746. [CrossRef] [PubMed]
3. Rakoff-Nahoum, S.; Foster, K.R.; Comstock, L.E. The Evolution of Cooperation within the Gut Microbiota. *Nature* **2016**, *533*, 255–259. [CrossRef]
4. Seo, D.-O.; Holtzman, D.M. Gut Microbiota: From the Forgotten Organ to a Potential Key Player in the Pathology of Alz-heimer's Disease. *J. Gerontol. A Biol. Sci. Med. Sci.* **2020**, *75*, 1232–1241. [CrossRef]
5. Salvucci, E. Microbiome, Holobiont and the Net of Life. *Crit. Rev. Microbiol.* **2016**, *42*, 485–494. [CrossRef]
6. Khosravi, A.; Mazmanian, S.K. Disruption of the gut microbiome as a risk factor for microbial infections. *Curr. Opin. Microbiol.* **2013**, *16*, 221–227. [CrossRef]
7. Thursby, E.; Juge, N. Introduction to the human gut microbiota. *Biochem. J.* **2017**, *474*, 1823–1836. [CrossRef]
8. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature* **2012**, *486*, 207–214. [CrossRef] [PubMed]
9. D'Argenio, V.; Salvatore, F. The role of the gut microbiome in the healthy adult status. *Clin. Chim. Acta* **2015**, *451*, 97–102. [CrossRef] [PubMed]
10. Qin, J.; Li, R.; Raes, J.; Arumugam, M.; Burgdorf, K.S.; Manichanh, C.; Nielsen, T.; Pons, N.; Levenez, F.; Yamada, T.; et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **2010**, *464*, 59–65. [CrossRef] [PubMed]
11. Salehi, B.; Dimitrijević, M.; Aleksić, A.; Neffe-Skocińska, K.; Zielińska, D.; Kołożyn-Krajewska, D.; Sharifi-Rad, J.; Stojanović-Radić, Z.; Prabu, S.M.; Rodrigues, C.F.; et al. Human microbiome and homeostasis: Insights into the key role of prebiotics, probiotics, and symbiotics. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 1415–1428. [CrossRef]
12. Rinninella, E.; Raoul, P.; Cintoni, M.; Franceschi, F.; Miggiano, G.A.D.; Gasbarrini, A.; Mele, M.C. What Is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms* **2019**, *7*, 14. [CrossRef]
13. Rolhion, N.; Chassaing, B. When pathogenic bacteria meet the intestinal microbiota. *Philos. Trans. R. Soc. B Biol. Sci.* **2016**, *371*, 20150504. [CrossRef] [PubMed]
14. Marques, F.Z.; Mackay, C.R.; Kaye, D.M. Beyond gut feelings: How the gut microbiota regulates blood pressure. *Nat. Rev. Cardiol.* **2018**, *15*, 20–32. [CrossRef]
15. Mouzaki, M.; Comelli, E.M.; Arendt, B.M.; Bonengel, J.; Fung, S.K.; Fischer, S.E.; McGilvray, I.D.; Allard, J.P. Intestinal microbiota in patients with nonalcoholic fatty liver disease. *Hepatology* **2013**, *58*, 120–127. [CrossRef] [PubMed]
16. Schwabe, R.F.; Jobin, C. The microbiome and cancer. *Nat. Rev. Cancer* **2013**, *13*, 800–812. [CrossRef] [PubMed]
17. Shahi, S.K.; Freedman, S.N.; Mangalam, A.K. Gut microbiome in multiple sclerosis: The players involved and the roles they play. *Gut Microbes* **2017**, *8*, 607–615. [CrossRef] [PubMed]
18. Shen, L.; Liu, L.; Ji, H.-F. Alzheimer's Disease Histological and Behavioral Manifestations in Transgenic Mice Correlate with Specific Gut Microbiome State. *J. Alzheimer's Dis.* **2017**, *56*, 385–390. [CrossRef] [PubMed]
19. Wen, L.; Ley, R.E.; Volchkov, P.Y.; Stranges, P.B.; Avanesyan, L.; Stonebraker, A.C.; Hu, C.; Wong, F.S.; Szot, G.L.; Blue-stone, J.A.; et al. Innate Immunity and Intestinal Microbiota in the Development of Type 1 Diabetes. *Nature* **2008**, *455*, 1109–1113. [CrossRef]
20. Liu, Y.-C.; Li, X.-Y.; Shen, L. Modulation effect of tea consumption on gut microbiota. *Appl. Microbiol. Biotechnol.* **2019**, *104*, 981–987. [CrossRef] [PubMed]
21. Barko, P.; McMichael, M.; Swanson, K.; Williams, D. The Gastrointestinal Microbiome: A Review. *J. Vet. Intern. Med.* **2017**, *32*, 9–25. [CrossRef] [PubMed]
22. Rothschild, D.; Weissbrod, O.; Barkan, E.; Kurilshikov, A.; Korem, T.; Zeevi, D.; Costea, P.I.; Godneva, A.; Kalka, I.N.; Bar, N.; et al. Environment dominates over host genetics in shaping human gut microbiota. *Nat. Cell Biol.* **2018**, *555*, 210–215. [CrossRef] [PubMed]
23. Zmora, N.; Suez, J.; Elinav, E. You are what you eat: Diet, health and the gut microbiota. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 35–56. [CrossRef] [PubMed]
24. Schmidt, T.S.; Raes, J.; Bork, P. The Human Gut Microbiome: From Association to Modulation. *Cell* **2018**, *172*, 1198–1215. [CrossRef]
25. Zhernakova, A.; Kurilshikov, A.; Bonder, M.J.; Tigchelaar, E.F.; Schirmer, M.; Vatanen, T.; Mujagic, Z.; Vila, A.V.; Falony, G.; Vieira-Silva, S.; et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science* **2016**, *352*, 565–569. [CrossRef] [PubMed]
26. Duda-Chodak, A.; Tarko, T.; Satora, P.; Sroka, P. Interaction of Dietary Compounds, Especially Polyphenols, with the Intes-tinal Microbiota: A Review. *Eur. J. Nutr.* **2015**, *54*, 325–341. [CrossRef] [PubMed]
27. Malongane, F.; McGaw, L.J.; Mudau, F.N. The synergistic potential of various teas, herbs and therapeutic drugs in health improvement: A review. *J. Sci. Food Agric.* **2017**, *97*, 4679–4689. [CrossRef]
28. Khan, N.; Mukhtar, H. Tea Polyphenols in Promotion of Human Health. *Nutrients* **2018**, *11*, 39. [CrossRef]

29. Neveu, V.; Perez-Jimenez, J.; Vos, F.; Crespy, V.; Du Chaffaut, L.; Mennen, L.; Knox, C.; Eisner, R.; Cruz, J.; Wishart, D.; et al. Phenol-Explorer: An online comprehensive database on polyphenol contents in foods. *Database* **2010**, *2010*, bap024. [CrossRef] [PubMed]
30. Espín, J.C.; González-Sarrías, A.; Tomás-Barberán, F.A. The gut microbiota: A key factor in the therapeutic effects of (poly)phenols. *Biochem. Pharmacol.* **2017**, *139*, 82–93. [CrossRef]
31. Marchesi, J.R.; Adams, D.H.; Fava, F.; Hermes, G.D.A.; Hirschfield, G.M.; Hold, G.; Quraishi, M.N.; Kinross, J.; Smidt, H.; Tuohy, K.M.; et al. The Gut Microbiota and Host Health: A New Clinical Frontier. *Gut* **2016**, *65*, 330–339. [CrossRef] [PubMed]
32. Henning, S.M.; Choo, J.J.; Heber, D. Nongallated Compared with Gallated Flavan-3-ols in Green and Black Tea Are More Bioavailable. *J. Nutr.* **2008**, *138*, 1529S–1534S. [CrossRef] [PubMed]
33. Almeida, A.F.; Dos Santos, C.N.; Ventura, M.R. Polyphenols, their Metabolites and Derivatives as Drug Leads. *Curr. Pharm. Des.* **2018**, *24*, 2188–2207. [CrossRef]
34. Ozdal, T.; Sela, D.A.; Xiao, J.; Boyacioglu, D.; Chen, F.; Capanoglu, E. The Reciprocal Interactions between Polyphenols and Gut Microbiota and Effects on Bioaccessibility. *Nutrients* **2016**, *8*, 78. [CrossRef] [PubMed]
35. Duda-Chodak, A. The inhibitory effect of polyphenols on human gut microbiota. *J. Physiol. Pharmacol.* **2012**, *63*, 497–503. [PubMed]
36. Danneskiold-Samsøe, N.B.; Dias de Freitas Queiroz Barros, H.; Santos, R.; Bicas, J.L.; Cazarin, C.B.B.; Madsen, L.; Kristiansen, K.; Pastore, G.M.; Brix, S.; Maróstica Júnior, M.R. Interplay between Food and Gut Microbiota in Health and Disease. *Food Res. Int.* **2019**, *115*, 23–31. [CrossRef] [PubMed]
37. Ivey, K.L.; Chan, A.T.; Izard, J.; Cassidy, A.; Rogers, G.B.; Rimm, E.B. Role of Dietary Flavonoid Compounds in Driving Patterns of Microbial Community Assembly. *mBio* **2019**, *10*, e01205-19. [CrossRef]
38. Cardona, F.; Andrés-Lacueva, C.; Tulipani, S.; Tinahones, F.J.; Queipo-Ortuño, M.I. Benefits of Polyphenols on Gut Microbiota and Implications in Human Health. *J. Nutr. Biochem.* **2013**, *24*, 1415–1422. [CrossRef]
39. Parkar, S.G.; Trower, T.M.; Stevenson, D.E. Fecal Microbial Metabolism of Polyphenols and Its Effects on Human Gut Microbiota. *Anaerobe* **2013**, *23*, 12–19. [CrossRef]
40. Selma, M.V.; Espín, J.C.; Tomás-Barberán, F.A. Interaction between Phenolics and Gut Microbiota: Role in Human Health. *J. Agric. Food Chem.* **2009**, *57*, 6485–6501. [CrossRef]
41. Cheng, M.; Zhang, X.; Miao, Y.; Cao, J.; Wu, Z.; Weng, P. The modulatory effect of (-)-epigallocatechin 3-O-(3-O-methyl) gallate (EGCG3″Me) on intestinal microbiota of high fat diet-induced obesity mice model. *Food Res. Int.* **2017**, *92*, 9–16. [CrossRef]
42. Chen, G.; Xie, M.; Wan, P.; Chen, D.; Dai, Z.; Ye, H.; Hu, B.; Zeng, X.; Liu, Z. Fuzhuan Brick Tea Polysaccharides Attenuate Metabolic Syndrome in High-Fat Diet Induced Mice in Association with Modulation in the Gut Microbiota. *J. Agric. Food Chem.* **2018**, *66*, 2783–2795. [CrossRef]
43. Cheng, M.; Zhang, X.; Zhu, J.; Cheng, L.; Cao, J.; Wu, Z.; Weng, P.; Zheng, X. A metagenomics approach to the intestinal microbiome structure and function in high fat diet-induced obesity mice fed with oolong tea polyphenols. *Food Funct.* **2018**, *9*, 1079–1087. [CrossRef]
44. Sun, H.; Chen, Y.; Cheng, M.; Zhang, X.; Zheng, X.; Zhang, Z. The modulatory effect of polyphenols from green tea, oolong tea and black tea on human intestinal microbiota in vitro. *J. Food Sci. Technol.* **2017**, *55*, 399–407. [CrossRef] [PubMed]
45. Cassotta, M.; Forbes-Hernández, T.Y.; Calderón Iglesias, R.; Ruiz, R.; Elexpuru Zabaleta, M.; Giampieri, F.; Battino, M. Links between nutrition, infectious diseases, and microbiota: Emerging technologies and opportunities for human-focused re-search. *Nutrients* **2020**, *12*, 1827. [CrossRef]
46. Perlman, R.L. Mouse Models of Human Disease: An Evolutionary Perspective. *Evol. Med. Public Health* **2016**, *2016*, eow014-6. [CrossRef]
47. Pham, V.; Mohajeri, M. The application of in vitro human intestinal models on the screening and development of pre- and probiotics. *Benef. Microbes* **2018**, *9*, 725–742. [CrossRef]
48. Van Norman, G.A. Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is It Time to Rethink Our Current Approach? *JACC Basic Transl. Sci.* **2019**, *4*, 845–854. [CrossRef] [PubMed]
49. Moher, D.; Jadad, A.R.; Tugwell, P. Assessing the Quality of Randomized Controlled Trials: Current Issues and Future Di-rections. *Int. J. Technol. Assess. Health Care* **1996**, *12*, 195–208. [CrossRef] [PubMed]
50. Zhou, Y.; Zhang, N.; Arikawa, A.Y.; Chen, C. Inhibitory Effects of Green Tea Polyphenols on Microbial Metabolism of Aro-matic Amino Acids in Humans Revealed by Metabolomic Analysis. *Metabolites* **2019**, *9*, 96. [CrossRef]
51. Mai, V.; Katki, H.A.; Harmsen, H.; Gallaher, D.; Schatzkin, A.; Baer, D.J.; Clevidence, B. Effects of a Controlled Diet and Black Tea Drinking on the Fecal Microflora Composition and the Fecal Bile Acid Profile of Human Volunteers in a Double-Blinded Randomized Feeding Study. *J. Nutr.* **2004**, *134*, 473–478. [CrossRef] [PubMed]
52. Janssens, P.L.H.R.; Penders, J.; Hursel, R.; Budding, A.E.; Savelkoul, P.H.M.; Westerterp-Plantenga, M.S. Long-Term Green Tea Supplementation Does Not Change the Human Gut Microbiota. *PLoS ONE* **2016**, *11*, e0153134. [CrossRef] [PubMed]
53. Yuan, X.; Long, Y.; Ji, Z.; Gao, J.; Fu, T.; Yan, M.; Zhang, L.; Su, H.; Zhang, W.; Wen, X.; et al. Green Tea Liquid Consumption Alters the Human Intestinal and Oral Microbiome. *Mol. Nutr. Food Res.* **2018**, *62*, e1800178. [CrossRef]
54. Huang, F.; Zheng, X.; Ma, X.; Jiang, R.; Zhou, W.; Zhou, S.; Zhang, Y.; Lei, S.; Wang, S.; Kuang, J.; et al. The-abrownin from Pu-Erh Tea Attenuates Hypercholesterolemia via Modulation of Gut Microbiota and Bile Acid Metabolism. *Nat. Commun.* **2019**, *10*, 4971. [CrossRef] [PubMed]

55. Jin, J.-S.; Touyama, M.; Hisada, T.; Benno, Y. Effects of Green Tea Consumption on Human Fecal Microbiota with Special Reference to Bifidobacterium Species: Effects of Green Tea on Fecal Microbiota. *Microbiol. Immunol.* **2012**, *56*, 729–739. [CrossRef]
56. Ahn, J.; Sinha, R.; Pei, Z.; Dominianni, C.; Wu, J.; Shi, J.; Goedert, J.J.; Hayes, R.B.; Yang, L. Human Gut Microbiome and Risk for Colorectal Cancer. *J. Natl. Cancer Inst.* **2013**, *105*, 1907–1911. [CrossRef]
57. Borges-Canha, M.; Portela-Cidade, J.P.; Dinis-Ribeiro, M.; Leite-Moreira, A.F.; Pimentel-Nunes, P. Role of Colonic Microbio-ta in Colorectal Carcinogenesis: A Systematic Review. *Rev. Esp. Enferm. Dig.* **2015**, *107*, 659–671. [CrossRef] [PubMed]
58. Hale, V.L.; Chen, J.; Johnson, S.; Harrington, S.C.; Yab, T.C.; Smyrk, T.C.; Nelson, H.; Boardman, L.A.; Druliner, B.R.; Levin, T.R.; et al. Shifts in the Fecal Microbiota Associated with Adenomatous Polyps. *Cancer Epidemiol. Biomark. Prev.* **2017**, *26*, 85–94. [CrossRef]
59. Russo, E.; Bacci, G.; Chiellini, C.; Fagorzi, C.; Niccolai, E.; Taddei, A.; Ricci, F.; Ringressi, M.N.; Borrelli, R.; Melli, F.; et al. Preliminary Comparison of Oral and Intestinal Human Microbiota in Patients with Colorectal Cancer: A Pilot Study. *Front. Microbiol.* **2017**, *8*, 2699. [CrossRef]
60. Zhang, H.-H.; Liu, J.; Lv, Y.-J.; Jiang, Y.-L.; Pan, J.-X.; Zhu, Y.-J.; Huang, M.-G.; Zhang, S.-K. Changes in Intestinal Microbio-ta of Type 2 Diabetes in Mice in Response to Dietary Supplementation with Instant Tea or Matcha. *Can. J. Diabetes* **2020**, *44*, 44–52. [CrossRef]
61. Wang, L.; Zeng, B.; Liu, Z.; Liao, Z.; Zhong, Q.; Gu, L.; Wei, H.; Fang, X. Green Tea Polyphenols Modulate Colonic Microbiota Diversity and Lipid Metabolism in High-Fat Diet Treated HFA Mice. *J. Food Sci.* **2018**, *83*, 864–873. [CrossRef]
62. Wang, L.; Zeng, B.; Zhang, X.; Liao, Z.; Gu, L.; Liu, Z.; Zhong, Q.; Wei, H.; Fang, X. The effect of green tea polyphenols on gut microbial diversity and fat deposition in C57BL/6J HFA mice. *Food Funct.* **2016**, *7*, 4956–4966. [CrossRef] [PubMed]
63. Jung, E.S.; Park, H.M.; Hyun, S.M.; Shon, J.C.; Singh, D.; Liu, K.-H.; Whon, T.W.; Bae, J.-W.; Hwang, J.S.; Lee, C.H. The green tea modulates large intestinal microbiome and exo/endogenous metabolome altered through chronic UVB-exposure. *PLoS ONE* **2017**, *12*, e0187154. [CrossRef]
64. Seo, D.-B.; Jeong, H.W.; Cho, D.; Lee, B.J.; Lee, J.H.; Choi, J.Y.; Bae, I.-H.; Lee, S.-J. Fermented Green Tea Extract Alleviates Obesity and Related Complications and Alters Gut Microbiota Composition in Diet-Induced Obese Mice. *J. Med. Food* **2015**, *18*, 549–556. [CrossRef] [PubMed]
65. Lu, X.; Liu, J.; Zhang, N.; Fu, Y.; Zhang, Z.; Li, Y.; Wang, W.; Li, Y.; Shen, P.; Cao, Y. Ripened Pu-erh Tea Extract Protects Mice from Obesity by Modulating Gut Microbiota Composition. *J. Agric. Food Chem.* **2019**, *67*, 6978–6994. [CrossRef] [PubMed]
66. Xia, Y.; Tan, D.; Akbary, R.; Kong, J.; Seviour, R.; Kong, Y. Aqueous raw and ripe Pu-erh tea extracts alleviate obesity and alter cecal microbiota composition and function in diet-induced obese rats. *Appl. Microbiol. Biotechnol.* **2019**, *103*, 1823–1835. [CrossRef]
67. Gao, X.; Xie, Q.; Kong, P.; Liu, L.; Sun, S.; Xiong, B.; Huang, B.; Yan, L.; Sheng, J.; Xiang, H. Polyphenol- and Caffeine-Rich Postfermented Pu-erh Tea Improves Diet-Induced Metabolic Syndrome by Remodeling Intestinal Homeostasis in Mice. *Infect. Immun.* **2017**, *86*, e00601-17. [CrossRef] [PubMed]
68. Foster, M.T.; Gentile, C.L.; Cox-York, K.; Wei, Y.; Wang, D.; Estrada, A.L.; Reese, L.; Miller, T.; Pagliassotti, M.J.; Weir, T.L. Fuzhuan tea consumption imparts hepatoprotective effects and alters intestinal microbiota in high saturated fat diet-fed rats. *Mol. Nutr. Food Res.* **2016**, *60*, 1213–1220. [CrossRef]
69. Henning, S.M.; Yang, J.; Hsu, M.; Lee, R.-P.; Grojean, E.M.; Ly, A.; Tseng, C.-H.; Heber, D.; Li, Z. Decaffeinated green and black tea polyphenols decrease weight gain and alter microbiome populations and function in diet-induced obese mice. *Eur. J. Nutr.* **2018**, *57*, 2759–2769. [CrossRef]
70. Liu, Z.; Chen, Z.; Guo, H.; He, D.; Zhao, H.; Wang, Z.; Zhang, W.; Liao, L.; Zhang, C.; Ni, L. The modulatory effect of infusions of green tea, oolong tea, and black tea on gut microbiota in high-fat-induced obese mice. *Food Funct.* **2016**, *7*, 4869–4879. [CrossRef]
71. Engelhardt, U.H. Tea Chemistry—What Do and What Don't We Know?—A Micro Review. *Food Res. Int.* **2020**, *132*, 109120. [CrossRef]
72. Yan, Z.; Zhong, Y.; Duan, Y.; Chen, Q.; Li, F. Antioxidant Mechanism of Tea Polyphenols and Its Impact on Health Benefits. *Anim. Nutr.* **2020**, *6*, 115–123. [CrossRef]
73. Anandh Babu, P.; Liu, D. Green Tea Catechins and Cardiovascular Health: An Update. *Curr. Med. Chem.* **2008**, *15*, 1840–1850. [CrossRef] [PubMed]
74. Cao, X.; Liu, M.; Hu, Y.; Xue, Q.; Yao, F.; Sun, J.; Sun, L.; Liu, Y. Systemic Characteristics of Biomarkers and Differential Me-tabolites of Raw and Ripened Pu-Erh Teas by Chemical Methods Combined with a UPLC-QQQ-MS-Based Metabolomic Ap-proach. *Lebenson. Wiss. Technol.* **2021**, *136*, 110316. [CrossRef]
75. Zhu, M.-Z.; Li, N.; Zhou, F.; Ouyang, J.; Lu, D.-M.; Xu, W.; Li, J.; Lin, H.-Y.; Zhang, Z.; Xiao, J.-B.; et al. Microbial bioconversion of the chemical components in dark tea. *Food Chem.* **2020**, *312*, 126043. [CrossRef]
76. Ning, J.; Li, D.; Luo, X.; Ding, D.; Song, Y.; Zhang, Z.; Wan, X. Stepwise Identification of Six Tea (*Camellia sinensis* (L.)) Categories Based on Catechins, Caffeine, and Theanine Contents Combined with Fisher Discriminant Analysis. *Food Anal. Methods* **2016**, *9*, 3242–3250. [CrossRef]
77. Yi, T.; Zhu, L.; Peng, W.-L.; He, X.-C.; Chen, H.-L.; Li, J.; Yu, T.; Liang, Z.-T.; Zhao, Z.-Z.; Chen, H.-B. Comparison of Ten Major Constituents in Seven Types of Processed Tea Using HPLC-DAD-MS Followed by Principal Component and Hierarchical Cluster Analysis. *Lebenson. Wiss. Technol.* **2015**, *62*, 194–201. [CrossRef]
78. Li, Q.; Chai, S.; Li, Y.; Huang, J.; Luo, Y.; Xiao, L.; Liu, Z. Biochemical Components Associated with Microbial Community Shift During the Pile-Fermentation of Primary Dark Tea. *Front. Microbiol.* **2018**, *9*, 1509. [CrossRef]

79. Li, Z.; Feng, C.; Luo, X.; Yao, H.; Zhang, D.; Zhang, T. Revealing the influence of microbiota on the quality of Pu-erh tea during fermentation process by shotgun metagenomic and metabolomic analysis. *Food Microbiol.* **2018**, *76*, 405–415. [CrossRef]
80. Lyu, C.; Chen, C.; Ge, F.; Liu, D.; Zhao, S.; Chen, D. A Preliminary Metagenomic Study of Puer Tea during Pile Fermentation: Metagenomic Study of Puer Tea during Pile Fermentation. *J. Sci. Food Agric.* **2013**, *93*, 3165–3174. [CrossRef]
81. Hasan, N.; Yang, H. Factors affecting the composition of the gut microbiota, and its modulation. *PeerJ* **2019**, *7*, e7502. [CrossRef]
82. Magne, F.; Gotteland, M.; Gauthier, L.; Zazueta, A.; Pesoa, S.; Navarrete, P.; Balamurugan, R. The Firmicutes/Bacteroidetes Ratio: A Relevant Marker of Gut Dysbiosis in Obese Patients? *Nutrients* **2020**, *12*, 1474. [CrossRef] [PubMed]
83. Stalmach, A.; Troufflard, S.; Serafini, M.; Crozier, A. Absorption, Metabolism and Excretion of Choladi Green Tea Fla-van-3-Ols by Humans. *Mol. Nutr. Food Res.* **2009**, *53* (Suppl. 1), S44–S53. [CrossRef]
84. Jalil, A.M.M.; Combet, E.; Edwards, C.A.; Garcia, A.L. Effect of β-Glucan and Black Tea in a Functional Bread on Short Chain Fatty Acid Production by the Gut Microbiota in a Gut Digestion/Fermentation Model. *Int. J. Environ. Res. Public Health* **2019**, *16*, 227. [CrossRef] [PubMed]
85. Donohoe, D.R.; Garge, N.; Zhang, X.; Sun, W.; O'Connell, T.M.; Bunger, M.K.; Bultman, S.J. The Microbiome and Butyrate Regulate Energy Metabolism and Autophagy in the Mammalian Colon. *Cell Metab.* **2011**, *13*, 517–526. [CrossRef] [PubMed]
86. Corrêa-Oliveira, R.; Fachi, J.L.; Vieira, A.; Sato, F.T.; Vinolo, M.A.R. Regulation of immune cell function by short-chain fatty acids. *Clin. Transl. Immunol.* **2016**, *5*, e73. [CrossRef] [PubMed]
87. Joossens, M.; Huys, G.; Cnockaert, M.; De Preter, V.; Verbeke, K.; Rutgeerts, P.; Vandamme, P.; Vermeire, S. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. *Gut* **2011**, *60*, 631–637. [CrossRef] [PubMed]
88. Kumari, R.; Ahuja, V.; Paul, J. Fluctuations in Butyrate-Producing Bacteria in Ulcerative Colitis Patients of North India. *World J. Gastroenterol.* **2013**, *19*, 3404–3414. [CrossRef] [PubMed]
89. Takahashi, M.; Ozaki, M.; Tsubosaka, M.; Kim, H.-K.; Sasaki, H.; Matsui, Y.; Hibi, M.; Osaki, N.; Miyashita, M.; Shibata, S. Effects of Timing of Acute and Consecutive Catechin Ingestion on Postprandial Glucose Metabolism in Mice and Hu-mans. *Nutrients* **2020**, *12*, 565. [CrossRef]
90. Wang, W.; Chen, L.; Zhou, R.; Wang, X.; Song, L.; Huang, S.; Wang, G.; Xia, B.; Forbes, B.A. Increased Proportions of Bifidobacterium and the Lactobacillus Group and Loss of Butyrate-Producing Bacteria in Inflammatory Bowel Disease. *J. Clin. Microbiol.* **2014**, *52*, 398–406. [CrossRef]
91. Pascal, V.; Pozuelo, M.; Borruel, N.; Casellas, F.; Campos, D.; Santiago, A.; Martinez, X.; Varela, E.; Sarrabayrouse, G.; Machiels, K.; et al. A microbial signature for Crohn's disease. *Gut* **2017**, *66*, 813–822. [CrossRef]
92. Nie, P.; Li, Z.; Wang, Y.; Zhang, Y.; Zhao, M.; Luo, J.; Du, S.; Deng, Z.; Chen, J.; Wang, Y.; et al. Gut Microbiome Interventions in Human Health and Diseases. *Med. Res. Rev.* **2019**, *39*, 2286–2313. [CrossRef] [PubMed]
93. Sandhu, K.V.; Sherwin, E.; Schellekens, H.; Stanton, C.; Dinan, T.G.; Cryan, J.F. Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsychiatry. *Transl. Res.* **2017**, *179*, 223–244. [CrossRef]
94. A David, L.; Materna, A.C.; Friedman, J.; I Campos-Baptista, M.; Blackburn, M.C.; Perrotta, A.; E Erdman, S.; Alm, E.J. Host lifestyle affects human microbiota on daily timescales. *Genome Biol.* **2014**, *15*, R89. [CrossRef] [PubMed]
95. Fraga, C.G.; Croft, K.D.; Kennedy, D.O.; Tomás-Barberán, F.A. The effects of polyphenols and other bioactives on human health. *Food Funct.* **2019**, *10*, 514–528. [CrossRef]
96. Hildebrandt, M.A.; Hoffmann, C.; Sherrill-Mix, S.A.; Keilbaugh, S.A.; Hamady, M.; Chen, Y.-Y.; Knight, R.; Ahima, R.S.; Bushman, F.; Wu, G.D. High-Fat Diet Determines the Composition of the Murine Gut Microbiome Independently of Obesity. *Gastroenterology* **2009**, *137*, 1716–1724. [CrossRef] [PubMed]
97. Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Microbial Ecology: Human Gut Microbes Associated with Obesity. *Nature* **2006**, *444*, 1022–1023. [CrossRef]
98. De Wit, N.; Derrien, M.; Bosch-Vermeulen, H.; Oosterink, E.; Keshtkar, S.; Duval, C.; Bosch, J.D.V.-V.D.; Kleerebezem, M.; Müller, M.; Van Der Meer, R. Saturated fat stimulates obesity and hepatic steatosis and affects gut microbiota composition by an enhanced overflow of dietary fat to the distal intestine. *Am. J. Physiol. Liver Physiol.* **2012**, *303*, G589–G599. [CrossRef] [PubMed]
99. De Bandt, J.-P.; Waligora-Dupriet, A.-J.; Butel, M.-J. Intestinal microbiota in inflammation and insulin resistance: Relevance to humans. *Curr. Opin. Clin. Nutr. Metab. Care* **2011**, *14*, 334–340. [CrossRef]
100. Zou, Y.; Ju, X.; Chen, W.; Yuan, J.; Wang, Z.; Aluko, R.E.; He, R. Rice bran attenuated obesity via alleviating dyslipidemia, browning of white adipocytes and modulating gut microbiota in high-fat diet-induced obese mice. *Food Funct.* **2020**, *11*, 2406–2417. [CrossRef]
101. Tseng, C.-H.; Wu, C.-Y. The gut microbiome in obesity. *J. Formos. Med. Assoc.* **2019**, *118*, S3–S9. [CrossRef]
102. Candela, M.; Biagi, E.; Maccaferri, S.; Turroni, S.; Brigidi, P. Intestinal Microbiota Is a Plastic Factor Responding to Environ-mental Changes. *Trends Microbiol.* **2012**, *20*, 385–391. [CrossRef]
103. Derrien, M.; Alvarez, A.-S.; de Vos, W.M. The Gut Microbiota in the First Decade of Life. *Trends Microbiol.* **2019**, *27*, 997–1010. [CrossRef] [PubMed]