

## DIETARY FACTORS AFFECTING *FIRMICUTES* AND *BACTEROIDETES* RATIO IN SOLVING OBESITY PROBLEM: A LITERATURE REVIEW

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### ABSTRACT

Obesity is caused by several factors. Gut microbiota composition is known to be one of the factors to play a role in modulating the obesity process. Nutrient factors and bioactive compounds from food can influence and help in modifying the gut microbiota composition, especially Firmicutes and Bacteroidetes. The purpose of this article is to discuss how significant the role of nutrients and other bioactive compounds on Firmicutes and Bacteroidetes ratio in solving the obesity problem. This article was compiled based on the literature search in the last ten years, related to nutrients and bioactive compounds influence Firmicutes/Bacteroidetes ratio in obesity. The results from several literature searches provided evidence that alteration in gut microbiota composition was linked to the increase of body weight through metabolic pathways, which was characterized by the increasing number of Firmicutes, the decreased number of Bacteroidetes, and an increase in Firmicutes/Bacteroidetes ratio. The increasing number of Firmicutes could induce short-chain fatty acid (SCFA) production and lead to more energy harvesting. Several dietary factors from fiber and amino acid, as well as bioactive compounds from an organic acid and polyphenol compounds, could influence the gut microbiota composition by reducing the Firmicutes level and increasing Bacteroidetes. The gut microbiota composition, especially Firmicutes and Bacteroidetes, could be induced by modifying diet enriched with fiber, polyphenol compounds, and other specified nutrients.

**Keywords:** obesity, dietary factors, gut microbiota, F/B ratio

### INTRODUCTION

The obesity problem has developed rapidly. Nowadays, obesity has become a global health problem that affects more than a third of the world's population. According to WHO (2015), 1.9 billion adolescents worldwide are categorized as overweight and 600 million adolescents are considered obese. The main causes of obesity are an increase in energy intake and low physical activity (Gerber, 2014; Whitney & Rolfes, 2013). Besides, environmental, psychological, genetic, and lifestyle factors also have implications in the development of obesity, including the role of gut microbiota (Gerber, 2014; Davis, 2016).

Gut microbiota is described as a collection of organisms that live in the human gastrointestinal tract. Most of the gut microbiota are included in the *Firmicutes* and *Bacteroidetes* phyla (Power *et al.*, 2014). The role of microbiota in the human body is to help in the food digestion process,

to regulate the immune system, and to provide the protection needed from pathogenic bacteria (Dietert, 2015). The microbiota composition of each individual varies and can change following age, diet, symbiotic consumption, antibiotics, drugs, disease condition, and genotypes (Chen *et al.*, 2014).

Moreover, gut microbiota, as the regulator of the digestion process, can affect and intervene in the metabolism process by increasing energy production from the diet and also regulating the composition of fatty acid tissue, which contributes to the obesity process (Cani *et al.*, 2012). Several studies stated that alteration in the gut microbiota composition (the increasing *Firmicutes* and *Bacteroidetes* ratio) which is influenced by dietary factors also plays a big role in the obesity process (Davis, 2016; Ley *et al.*, 2006). A diet which contains the low-fat polysaccharide to a diet high in fat and sugar alters the structure and the

composition of the gut microbiota which can also affect the metabolic pathways and microbiome gene expression (Moschen *et al.*, 2012). Dietary factors, such as the nutrients and bioactive compound from food, contributes to the direct and indirect effects on the gut microbiota. Dietary factors can directly promote or inhibit the microbiota growth, and increase the capability to harvest energy (Korem *et al.*, 2015). Also, bioactive compounds from food can indirectly shape the gut microbiota and affect the immunity (Li *et al.*, 2011). For instance, vitamin D is required to be the protection of gut mucosal defense against pathogens (Su *et al.*, 2016).

*Firmicutes* and *Bacteroidetes* ratio tends to increase in people with obesity and overweight (Kasai, 2015). The study conducted by Ley *et al.* (2006) obtained that a diet with low-calorie composition in obese subjects changed the balance of the *Firmicutes* and *Bacteroidetes* ratio, or the F/B ratio, to a level comparable to individuals with normal weight. F/B ratio is related to the increase of energy production from the fermentation in the colon which can cause the increase of SCFA production and contribute more energy. Another study by De Filippo *et al.* (2010) stated that there were differences in the F/B ratio in African children, who consumed food high in low-fat fiber, and Italian children, who consumed food high in fat and protein. The F/B ratio decreased with weight loss because of the low-calorie diet intake. These results emphasize that diet and

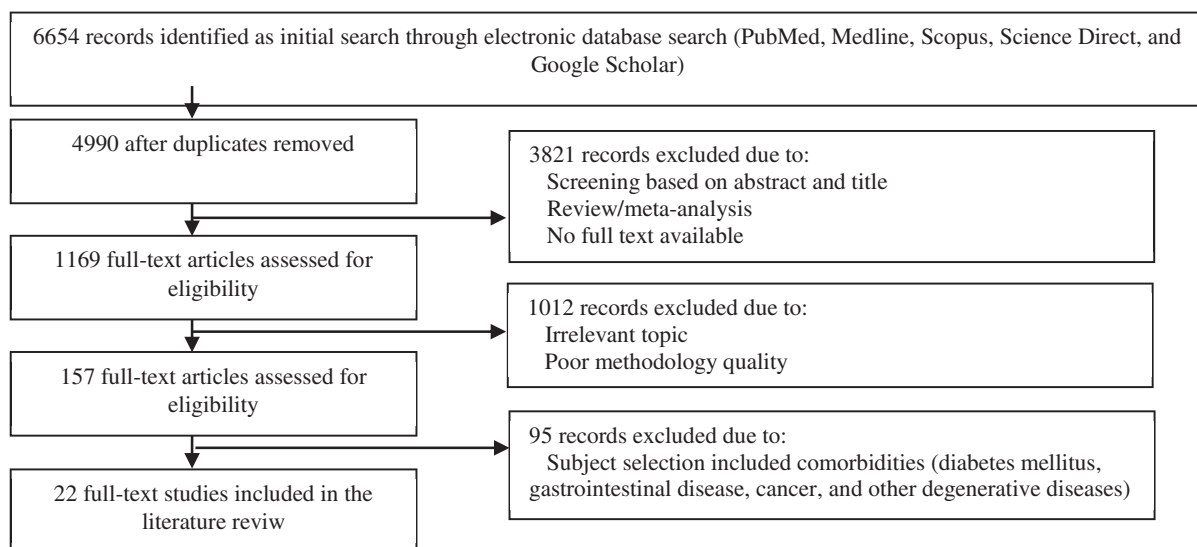
nutrient intake influence the formation of the gut microbiota composition (Scott *et al.*, 2008). Some other studies also show that food or diet is the source of energy for gut microbiota which can affect and have implications for the balance and functions of the human body (Graf *et al.*, 2015). Gut microbiota also has rapid responses to changes in diet and dietary habits (David *et al.*, 2014).

This review focuses on the current evidence of the association between F/B ratio and obesity as well as the dietary factors influencing the changes of it, also to discuss the role and influence of dietary factors (nutrients and bioactive compounds from food) in solving the obesity problem through the gut microbiota composition, which is F/B ratio.

## METHODS

The literature search was carried out on research articles (including observational studies namely cross-sectional, cohort, case-control, and experimental studies) within the last ten years (2009-2019) using the electronic database

PubMed/Medline, Scopus, Science Direct, and Google Scholar. Researches published before the period were also included in relevancy and can be justified. The main keyword used in the search for literature studies are diet; obesity; dietary factors; and gut microbiota, or *Firmicutes/Bacteroidetes* in open- and closed-access international journals and written in English. The researches chosen



**Figure 1.** Diagram flow of included and excluded studies for the review

must meet the inclusion criteria which show the role and influence of dietary factors in obesity and gut microbiota, both in human and animal studies. The study was excluded if the subject selection included other comorbidities such as diabetes mellitus, gastrointestinal disease, cancer, and other degenerative diseases, and if the study was also literature, systematic review, or meta-analysis. All articles found and chosen were then studied profoundly.

## RESULTS AND DISCUSSIONS

### Literature Search

A total of 22 research studies results were included in the review and further explained in Tables 1 and 2. Ten articles were analyzed according to the association between the F/B ratio and obesity, while twelve articles were analyzed regarding the dietary role in the alteration of the F/B ratio.

### Association of F/B ratio and Obesity

Obesity is known as a disorder caused by various factors, one of them is the energy imbalance, namely energy intake that exceeds the individual's energy expenditure (Hill *et al.*, 2012). Gut microbiota is known to have an important role in regulating energy balance (Apovian, 2016). The human gut is composed of five phyla, namely *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. Mainly, *Bacteroidetes* and *Firmicutes* are the ones dominating it around 90% of the total species (Qin *et al.*, 2010; Tang *et al.*, 2017). This composition of gut microbiota can alter between lean and obese individuals. Obese and lean individuals have different compositions of microbiota, especially the differences in the ability to convert the energy from food which is then stored as fat (Turnbaugh *et al.*, 2009). Alteration in the microbiota composition is one of the causes of obesity; one of them is a significant change in the composition of gram-positive microbiota, or *Firmicutes*, and gram-negative microbiota, or *Bacteroidetes* (Sonnenburg *et al.*, 2016).

Research conducted by Koliada *et al.* (2017) stated that the composition of *Firmicutes* increases and *Bacteroidetes* decreases with an increase in

Body Mass Index (BMI). *Firmicutes* increase the effectiveness in the calorie absorption by modulating and increasing the capacity for energy harvesting and the metabolic degradation rate of a given energy source, which results in more weight gain (Turnbaugh *et al.*, 2006; Krajmalnik-Brown *et al.*, 2012). Moreover, the increasing abundance of *Firmicutes* can also increase the number of lipid droplets which will increase the absorption of fatty acid. Microbiota can affect the increasing rate of host metabolism by modifying the production of bile salt and enhancing more fatty acid absorbed (Semova *et al.*, 2012; Swann *et al.*, 2011). These results are in accordance with the research conducted by Kasai *et al.* (2015), Riva *et al.* (2017) Ismail *et al.* (2010) Hou *et al.* (2017) Louis *et al.* (2016) and Andoh *et al.* (2016), in which the abundance of *Bacteroidetes* in obese individuals are lower, while *Firmicutes* and the F/B ratio in obese individuals are higher than in non-obese individuals. The research conducted by Ley *et al.* (2006) also stated that *Bacteroidetes* and *Firmicutes* are the phyla that dominated the microbiota composition in obese individuals. Before the intervention of the weight loss diet program, *Bacteroidetes* composition is less and dominated by *Firmicutes*. But, after the administration of diet, the composition of *Bacteroidetes* increases and *Firmicutes* decreases.

The diversity in the microbiota composition is also found to be significantly higher in obese individuals. The bacteria *Blautia hydrogenotrophica*, *Coprococcus catus*, *Eubacterium ventriosum*, *Ruminococcus bromii*, and *Ruminococcus obeum* are part of the phylum *Firmicutes* which is significantly associated with the obesity incidence. Those bacteria can degrade starch or polysaccharides, and other non-digestible dietary nutrient sources, such as pectin and cellulose. These nutrients will be fermented and the result is the production of short-chain fatty acids (SCFAs), mainly butyrate, propionate, and acetate, which can be used to produce more energy than *Bacteroidetes* (Turnbaugh *et al.*, 2006). SCFAs contribute approximately 200 kcal per day (Krebs *et al.*, 2002). The elevation level of SCFAs can both be protective and be the risk factor of obesity. The phylum *Bacteroidetes* dominantly produces acetate and propionate, whereas the phylum

*Firmicutes* produce butyrate. Butyrate is used as an energy source for colonic epithelium, insulin sensitivity in mice, anti-inflammatory in humans, colon carcinoma protection, gene-expression of leptin, and protection against diet-induced obesity. Acetate contributes to gluconeogenesis, as well as propionate. Also, higher fecal SCFA concentrations may reflect a protective mechanism against obesity (Graham *et al.*, 2015).

Moreover, these bacteria also carry genes in terms of enzymes such as CAZymes (carbohydrate-active enzymes) that play a role in the metabolism of polysaccharides, so that they can increase the efficiency of the energy production (Cantarel *et al.*, 2012). A high abundance of *Firmicutes* is associated with an increase in energy extraction, which escalates the amount of energy intake (Beh *et al.*, 2016). In non-obese individuals, specific bacterial species are included in the phylum *Bacteroidetes*, such as *Bacteroides faecichinchillae*, *Bacteroides thetaiotaomicron*, *Blautia wexlerae*, *Clostridium bolteae*, and *Flavonifractor plautii*, in which these bacteria are not found in obese individuals which can also be used as a decrease marker of metabolic syndrome (Kasai *et al.*, 2015; Upadhyaya *et al.*, 2016). However, *Bacteroidetes* are also linked with reduced body mass (De Filippo *et al.*, 2010).

The concentrations of fecal SCFAs tend to increase in obese individuals (Schwiertz *et al.*, 2010; Teixeira *et al.*, 2013). This occurs because of the decrease in the SCFA absorption in the colon. The concentrations of fecal SCFAs are used as a determinant of the balance between production and absorption of SCFA in the colon (Vogt *et al.*, 2003). Colonic fermentation is a process which requires the interaction between microbes and involves the degradation of nutrients, such as complex carbohydrate, dietary fiber, and protein through an anaerobic pathway (Macfarlane *et al.*, 1990; Cummings *et al.*, 1983; Smith *et al.*, 1979). The final results of the process are SCFAs, including acetate, propionate, butyrate, hydrogen, carbon dioxide, methane, and energy (Topping *et al.*, 2001; Cummings *et al.*, 1981; Miller *et al.*, 1979; Cummings *et al.*, 1991). These final products are required for gut microbiota to carry out cellular function. SCFA concentrations are produced as much as 5-10% of total energy intake

and may modulate body weight and obesity (Kasai *et al.*, 2015). The greater the efficiency of energy extraction from microbiota, the higher the risk of obesity in an individual. The research conducted by Fernandes *et al.* (2018) showed that the number of *Bacteroidetes* was inversely associated to BMI; meanwhile, there was a positive association between the F/B ratio and SCFA concentrations; also, there was a negative association between the abundance of *Bacteroidetes* and SCFA concentrations. According to Turnbaugh *et al.* (2006), the difference in the higher F/B ratio was associated with the elevated energy production from the colonic fermentation and caused the increase of SCFA production.

SCFAs have various roles; one of them is to take part in fat and glucose metabolism (Blaut & Clavel, 2007; Lin *et al.*, 2012). SCFA is a ligand for 2-paired receptors, GPR41 and GPR43, in which both receptors have different affinities. The GPR41 receptors have the highest affinity for propionic, butyric, and acetic acids, while the GPR43 receptors have the same affinity for the three acids. The bond of SCFAs, especially the bond of propionic acid and GPR41 receptors, will increase the expression of leptin, while the bond between acetic acid and GPR43 receptors will increase the secretion of leptin in the fat tissue (Backhed *et al.*, 2004; Arora *et al.*, 2011; Nie *et al.*, 2018). SCFAs can be an effective strategy in preventing weight gain which can be inhibited by supplementation of acetate, propionate, and butyrate. The study by Degen *et al.* (2005) showed that SCFAs could become the factor to affect lipogenesis and could assist in the secretion of peptide YY (PYY), which plays a role in the regulation of appetite and food intake. Moreover, SCFA supplementation can affect the gut microbiota composition in the feces by reducing the number of *Firmicutes* and increasing the number of *Bacteroidetes* (Spiller *et al.*, 1980).

The research conducted by Ismail *et al.* (2010) stated that gut microbiota contributed to the obesity process. The study results found that the high sensitivity C-reactive protein (hs-CRP) increased in obese individuals. This can occur since the increase in C-reactive protein level was caused by the high levels of interleukin-6 (IL6) in the adipose tissue and the release of IL-6 into the peripheral blood circulation (Cani *et al.*, 2008). Gut

**Table 1.** Association between Firmicutes/Bacteroidetes Ratio with Obesity Problem

| Research Title and Author   | Subjects  | Method  | Result   |
|---|---|---|--|
| Association between body mass index and <i>Firmicutes</i> / <i>Bacteroidetes</i> ratio in an adult Ukrainian population (Koliada et al., 2017)  | 61 healthy subjects, divided into 4 groups based on BMI.                                  | Design: cross sectional.<br>Analysis: DNA fecal samples were extracted and analyzed using qPCR using primers <i>Firmicutes</i> , <i>Actinobacteria</i> , and <i>Bacteroidetes</i> bacteria.   | <i>Firmicutes</i> increased and <i>Bacteroidetes</i> decrease with increasing BMI. F/B ratio also increased with increasing BMI (OR=1.23).   |
| Frequency of <i>Firmicutes</i> and <i>Bacteroidetes</i> in gut microbiota in obese and normal weight Egyptian children and adults (Ismail et al., 2011)   | 79 subjects, with 51 obese individuals and 28 individuals of normal weight.               | Design: cross sectional.<br>Analysis: Fecal samples were collected. Total DNA was extracted from collected stool samples and analyzed using qPCR with primer <i>Firmicutes</i> and <i>Bacteroidetes</i> bacteria.                                 | The proportions of <i>Firmicutes</i> and <i>Bacteroidetes</i> increased in obese group (p<0.001). There was a significant positive trend for hsCRP in subjects with higher levels of <i>Firmicutes</i> (p=0.004).        |
| Comparison of the gut microbiota composition between obese and non-obese individuals in a Japanese population, as analyzed by terminal restriction fragment length polymorphism and next-generation sequencing (Kasai et al., 2015) | 56 subjects, 23 obese subjects and 33 subjects of normal weight.                          | Design: cross sectional.<br>Analysis: Fecal samples were collected. Gut microbiota were evaluated using T-RFLP analysis. Microbiota diversity was counted using Shannon-Weiner diversity index (H') for pylotypes number (richness and evenness). | T-RFLP showed a significant reduction of <i>Bacteroidetes</i> and an increase of F/B ratio on obese individuals compared to non-obese (p<0.05). Gut microbiota diversity on obese individuals was significantly greater. |
| Adiposity, gut microbiota, and faecal short chain fatty acids are linked in adult human (Fernandes et al., 2014)  | 94 subjects divided to 52 lean subjects (LN) and 42 overweight and obese subjects (OWOB). | Design: cross sectional<br>Analysis: extract of fecal bacterial DNA was analyzed by RT PCR using primers of bacteria <i>C. occoides</i> and <i>C. leptum</i>  | Overweight and obese subjects had higher total SCFA (p=0.002) than lean subjects. F/B ratio was shown to be positively correlated with total SCFA (r=0.42; p<0.0001).  |
| Human gut microbiota associated with obesity in Chinese children and adolescents (Hou et al., 2017)   | 87 obese children and 56 non obese children in age of 3-18 years old.                     | Design: cohort 90 days<br>Analysis: extract of fecal bacterial DNA was analyzed by PCR, taxonomic analysis (OTU and QIME), and metagenomic.   | F/B ratio in obese subjects was higher than in non-obese subjects.   |
| Characterization of the gut microbial community of obese patients following a weight loss intervention using whole metagenome shotgun sequencing (Louis et al., 2016)   | 16 subjects joined in the weight loss program.  | Design: cross sectional.<br>Analysis: extract of fecal bacterial DNA was analyzed using taxonomic analysis and metagenomic using DNA shotgun sequencing.  | F/B ratio was higher in obese subjects with metabolic syndrome (0.64) than in healthy obese subjects (0.27).   |
| Comparison of the gut microbial community between obese and lean peoples using 16s gene sequencing in a Japanese population (Andoh et al., 2016)  | 10 obese subjects and 10 lean subjects.   | Design: cross sectional.<br>Analysis: extract of fecal bacterial DNA was analyzed by 16s rRNA sequence using Illumina MiSeq II system.  | The number of Firmicutes was higher in obese group (p<0.01). The number of Bacteroidetes and F/B ratio are not significantly different in both groups.   |
| Bacterial microbiota and fatty acids in the faeces of overweight and obese children (Barczynska et al., 2018)   | 20 obese children and 20 children of normal weight.                                       | Design: case control.<br>Analysis: extract of fecal bacterial DNA was analyzed by RFLP and DNA sequencing.  | <i>Firmicutes</i> dominated the fecal bacteria kind in obese children, whereas <i>Bacteroidetes</i> became minority (p<0.001). The number of SCFA was lower in obese children.   |
| Pediatric obesity is associated with an altered gut microbiota and discordant shifts in <i>Firmicutes</i> population (Riva et al., 2017)  | 36 children of normal weight and 42 obese children in age of 6-16 years old.              | Design: cohort.<br>Analysis: extract of fecal bacterial DNA was analyzed by DNA sequencing.   | Obesity was correlated with the elevation of <i>Firmicutes</i> and the reduction of <i>Bacteroidetes</i> .   |
| Differences in gut microbiota composition between obese and lean children: a cross-sectional study (Bervoets et al., 2013)  | 26 overweight children and 27 lean children in age of 6-16 years old.                     | Design: cross sectional.<br>Analysis: extract of fecal bacterial DNA was analyzed by qPCR using primers of <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Clostridium</i> , <i>Lactobacillus</i> , and <i>Staphylococcus</i> .                  | Obese children showed an increase of F/B ratio. The proportion of <i>B. vulgatus</i> was much lower and <i>Lactobacillus</i> was higher. <i>Lactobacillus</i> in obese children had positive correlation with hsCRP.     |

microbiota has a role in handling the inflammation condition by regulating lipopolysaccharide (LPS) concentration which triggers inflammation and the onset of obesity. This result is also shown in the study by Cani *et al.* (2007). The subcutaneous infusion of LPS can cause weight gain and insulin resistance in mice without changing the energy intake. The research conducted by Bervoets *et al.* (2013) also stated that *Lactobacillus spp.* was associated with hs-CRP levels in children and obese adults, so that the role of *Lactobacillus spp.* could affect the decrease of the inflammatory process in the obesity problem.

### **The Role of Dietary Factors in the Balance of Firmicutes and Bacteroidetes Ratio**

Nutrients and bioactive compounds can be one of the factors which can influence the gut microbiota composition. Specific nutrients such as dietary fiber and amino acid have significant roles in the balance of gut microbiota. Moreover, the gut microbiota balance can also be affected by both prebiotics, probiotics, and polyphenol compounds found in food (Kishimoto *et al.*, 2007; Flint *et al.*, 2012).

#### **Fiber**

Obesity is caused by an energy imbalance between energy intake and expenditure. Soluble dietary fiber can promote energy balance (Brown *et al.*, 1999; Chandalia *et al.*, 2000; De Vadder *et al.*, 2014). The research conducted by Wang *et al.* (2018) showed that obese mice given dietary fiber intake for 9 weeks had reduced weight gain. Dietary fiber intake can help to reduce fat mass and the size of adipose tissue, as well as to increase energy. This study found that soluble dietary fiber intake increased the energy expenditure through the experiment from mice induced by high-fat diet and fiber resulted in the elevation of energy expenditure. The change in gut microbiota composition such as the decrease of F/B ratio can be associated with the weight loss induced by dietary fiber intake. The number and type of fiber are calculated based on gut microbiota composition and SCFA production (Macfarlane *et al.*, 1995; Royall *et al.*, 1990). The obesity protection mechanism from the dietary fiber is through the SCFA regulation which will secrete

gut hormone peptide YY (PYY) in the intestine to help in regulating food intake and processing energy balance (Freeland *et al.*, 2010; Tarini *et al.*, 2010; Samuel *et al.*, 2008). Table 1 explains that an increase in the abundance of *Firmicutes* and an increase in the F/B ratio are closely correlated with the obesity problem, whereas an increase in *Bacteroidetes* is correlated with weight loss. Obese mice given a high dietary fiber intake showed an increase in the number of *Bacteroidetes*. Changes in the composition of this microbiota are correlated with weight loss, which becomes the effect of soluble dietary fiber intake.

Intervention research was also conducted by Dong *et al.* (2016) to compare the effects of three oat products, including oatmeal (OM), oat flour (OF), and high-fiber oat bran (OB) on lipid metabolism and intestinal microbiota structure in obese mice. Oat products are known to be able to reduce body weight and reduce the LDL serum level. This can occur because of the role of  $\beta$ -glucan, which is one of the non-starch polysaccharides types. The  $\beta$ -glucan compound can increase the abundance of *Lactobacillus* and *Bifidobacterium*, and also can reduce the number of pathogenic bacteria such as *Enterobacter*. The analysis using PCA showed that oat products can change the structure and composition of the microbiota as a whole. Mice given all three oat products had the low F/B ratio and lower *Firmicutes* compared to obese mice given only a diet. Total fiber,  $\beta$ -glucan, and starch in OB products (9.87%) did not undergo the metabolism in the small intestine and went through the fermentation process in the intestine, thereby maximizing the modification of gut microbiota composition and SCFA production, inhibiting weight gain and fat accumulation, as well as improving serum lipid and inflammation process (Nielsen *et al.*, 2015).

Fiber and flavonoid sources from fruits and vegetables can assist in reducing the abundance of *Firmicutes* and elevating the abundance of *Bacteroidetes*. Fruits and vegetables contain bioactive compounds that can improve health status and reduce the risk of disease, as well as regulate the gut microbiota composition. Phenolic compounds and fiber are most commonly found in fruits and vegetables. Administration of fruit

and vegetable juice is correlated with a decreased proportion of *Firmicutes* and an increasing proportion of *Bacteroidetes* (Henning, 2017). Carbohydrate complex supplementation, as in the type of pectin, which comes from apples is known to promote normalizing the level of *Bacteroidetes* and *Firmicutes* in high fat diet-induced mice. Pectin supplementation also lowers the level of endotoxin and reduces the inflammatory factors, such as TNF- $\alpha$  and IL-6 (Jiang *et al.*, 2016). Dietary fiber intake from whole grains can also influence the reduction of *Firmicutes* as well as the elevation of *Bacteroidetes* and *Lactobacillus*, which can also lower the risk of inflammation (Vitaglione *et al.*, 2015).

### **Polyphenol Compounds**

Anthocyanin is one of the flavonoids that can regulate the microbiota composition and the gastrointestinal system. Jamar *et al.* (2017) stated that anthocyanin had an anti-obesity effect related to microbiota regulation. The research conducted by Hester *et al.* (2018) provided the intervention of anthocyanin and prebiotic fiber blend supplementation. After 8 weeks of intervention, it was found that there was a decrease in the number of *Firmicutes*, *Actinobacteria*, and F/B ratio, and a significant increase in the number of *Bacteroidetes*. The limitation of this study is that there was still no clear evidence and description of the role of specific bioactive compounds which influenced the most on the changes of gut microbiota composition.

Fermented food also has an anti-obesity effect, through changes in microbiota composition and gene expression associated with the metabolic syndrome process. The research conducted by Han *et al.* (2015) showed that subjects who consumed kimchi (fermented vegetables) experienced a decrease in the F/B ratio. Moreover, consumption of fermented products such as vinegar, which mostly contain acetic acid and other bioactive compounds, can protect and prevent hypertension, hypercholesterolemia, hyperglycemia, antimicrobial, and anticancer (Mohamad *et al.*, 2015). The research conducted by Beh *et al.* (2017) also showed the intervention of synthetic acetic acid vinegar and Nipa vinegar can significantly reduce the F/B ratio and increase *Bacteroidetes*,

*Lactobacillus*, *Parabacteroides*, *Akkermansia*, *Proteobacteria*, and *Oscillospira*. *Firmicutes* were able to ferment unabsorbed nutrients, namely fermented food, in the gut and increased *Bacteroidetes* in the gut (Beh *et al.*, 2016). Both synthetic acetic acid vinegar and Nipa vinegar were able to reduce the food intake of obese mice and alter the gut microbiota composition, which contributed to weight loss. In this study, fermented Nipa vinegar was considered superior to synthetic acetic acid vinegar in its benefits for weight loss, the hyperlipidemia effect, and the hepatoprotective effect due to the presence of phenolic metabolites, namely gallic acid and protocatechuic acid. These phenolic compounds are correlated with anti-inflammatory effects and can assist in restoring oxidative stress caused by obesity and liver inflammation.

### **Amino Acid**

The administration of amino acid glutamine based on de Souza *et al.* (2015) can reduce the F/B ratio, with a decrease in the number of *Firmicutes* and an increase in *Bacteroidetes*. This study showed that the effects of glutamine supplementation on gut microbiota composition were similar to individuals who experienced weight loss. However, this study did not show a significant difference in the number of *Bacteroidetes* in the groups given alanine and glutamine, since both groups experienced a decrease in the number of *Bacteroidetes*. The group given glutamine experienced a decreased number of *Firmicutes* more than another. The administration of glutamine supplementation can also reduce inflammatory factors, such as TNF- $\alpha$  and IL-6 in serum and peripheral tissue (Greenfield *et al.*, 2013; Prada *et al.*, 2007). In this study, the amount of *Veillonella* decreased after glutamine supplementation, which also became a marker for inflammation (De Filippo *et al.*, 2010).

### **Prebiotics**

Prebiotics are beneficial for the regulation of the gut microbiota composition and metabolism (Roberfroid, 2007; Parnell, 2012; Delzenne, 2003). Prebiotics are known to be able to alter the *Firmicutes* and *Bacteroidetes* composition (Okazaki *et al.*, 2016). Prebiotics compound from

**Table 2.** The Role of Dietary Factors in Modifying Firmicutes/Bacteroidetes Ratio

| Research Title and Author  | Subjects   | Method  | Result  |
|--|--|---|---|
| Soluble dietary fiber improves energy homeostasis in obese mice by remodeling the gut microbiota (Wang <i>et al.</i> , 2018)   | WT (wild type) mice was fed with high fat diet until it reached obesity.                       | Design: RCT intervention 2% of soluble dietary fiber.<br>Analysis: extract of fecal bacterial DNA was collected to determine gut microbiota using 16s rRNA sequencing using Illumina MiSeq platform.                        | Soluble dietary fiber lowered the number of <i>Firmicutes</i> and increased the number of <i>Bacteroidetes</i> , so that F/B was decreased in obese mice.   |
| Anti-obesity and anti-inflammatory effects of synthetic acetic acid vinegar and Nipa vinegar on high-fat-diet-induced obese mice (Beh <i>et al.</i> , 2017)  | 36 C57BL/6 mice were fed with high fat diet for 33 weeks.                                      | Design: RCT intervention with synthetic acetic acid vinegar and Nipa vinegar.<br>Analysis: extract of fecal bacterial DNA was used to analyze by using 16s rRNA metagenomic sequencing.                                     | Synthetic acetic acid vinegar and Nipa vinegar lowered the F/B ratio. A significant increase of <i>Bacteroides</i> , <i>Lactobacillus</i> , <i>Akkermansia</i> , <i>Parabacteroides</i> , and <i>Proteobacteria</i> (p<0.05).                   |
| Oat products modulate the gut microbiota and produce anti-obesity effects in obese rats (Dong <i>et al.</i> , 2016)  | 80 SD (Sprague-Dawley) mice were fed with high fat diet for 6 weeks.                           | Design: RCT intervention with oat meal (OM), oat flour (OF), and high fiber oat bran (OB).<br>Analysis: extract of fecal bacterial DNA was analyzed by PCR and phylogenetic.  | Three oat products altered the structure of gut microbiota, especially an increase of <i>Bacteroidetes</i> , a decrease of <i>Firmicutes</i> , and F/B ratio (p<0.05).  |
| Efficacy of an anthocyanin and prebiotic blend on intestinal environment in obese male and female subjects (Hester <i>et al.</i> , 2018)   | Subjects aged 18-50 years old with BMI 29.9-39.9 kg/m <sup>2</sup>                             | Design: RCT intervention with supplementation of 215 mg extract of anthocyanin and 2.7 gram prebiotic fiber (inulin from FOS).<br>Analysis: extract of fecal bacterial DNA was analyzed by sequence analysis and taxonomic. | There was a significant decrease of <i>Firmicutes</i> (74.9% to 59%), <i>Actinobacteria</i> , F/B ratio (14.2% to 9.3%), and also an increase of <i>Bacteroidetes</i> (13.8% to 34.5%) (p<0.001).   |
| Oral supplementation with L-glutamine alters gut microbiota of obese and overweight adults: a pilot study (deSouza <i>et al.</i> , 2015)   | 33 overweight and obese subjects, aged 23-59 years old.  | Design: RCT intervention with supplementation of 30 gram L-alanine or 30 gram L glutamine for 14 weeks.<br>Analysis: extract of fecal bacterial DNA was analyzed by new-generation sequencing.                              | Group administered with L-glutamine showed a significant decrease F/B ratio (0.85 to 0.57), whereas the group administered with L-alanine showed a significant increase of F/B ratio (0.91 to 1.12).  |
| Consumption of lily bulb modulates fecal ratios of <i>Firmicutes</i> and <i>Bacteroidetes</i> phyla in rats fed a high-fat diet (Okazaki <i>et al.</i> , 2016)   | SD mice aged 4 weeks old were fed with high fat diet.  | Design: RCT intervention with 7% RLB, 7% SLB, 0.9% extract of ethanol, or 6.1% extract of ethanol LB residue.<br>Analysis: extract of fecal bacterial DNA was analyzed by qPCR.   | There was a decrease of <i>Firmicutes</i> and an increase of <i>Bacteroidetes</i> in RLB and SLB groups. F/B ratio was not much influenced by ethanol extract or LB residual extract.   |
| Health benefit of vegetable/fruit juice-based diet: role of microbiome (Henning <i>et al.</i> , 2017)  | 25 healthy adolescents, aged 18-50 years old.  | Design: RCT intervention for 3 days of fruit/vegetables juice.<br>Analysis: extract of fecal bacterial DNA was analyzed by sequence analysis and taxonomic.   | There was a decrease of <i>Firmicutes</i> and <i>Proteobacteria</i> proportion. There was an increase of <i>Bacteroidetes</i> and <i>Cyanobacteria</i> .  |
| Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber (Vitaglione <i>et al.</i> , 2015) | 80 overweight/obese subjects with low intake of fruits and vegetables and sedentary lifestyle. | Design: RCT intervention with whole grain wheat (WG) or refined wheat (RW) for 8 weeks.<br>Analysis: extract of fecal bacterial DNA was analyzed by PCR sequence and taxonomic (QIME and OTU).                              | Whole grain consumption increased <i>Bacteroidetes</i> and <i>Firmicutes</i> but decreased <i>Clostridium</i> . There was an increase of DHFA (4 times) and fecal ferulic acid. There was a decrease of TNF- $\alpha$ and an increase of IL-10. |



| Research Title and Author  | Subjects  | Method  | Result   |
|--|---|---|--|
| Reinforcement of intestinal epithelial barrier by arabinoxylans in overweight and obese subjects: a randomized controlled trial arabinoxylans in gut barrier (Salden <i>et al.</i> , 2018) | 47 overweight/ obese subjects aged 18-70 years old, BMI 28-35 kg/m <sup>2</sup> | Design: RCT intervention 7.9 gram/day of arabinoxylans (AX) and 15 gram/day of AX.<br>Analysis: extract of fecal bacterial DNA was analyzed by 16s rRNA sequencing using Illumina MiSeq platform. | There was no significant differences in the number of <i>Firmicutes</i> and <i>Bacteroidetes</i> in six weeks. But, there was a decrease in diversity, fecal pH, and an increase in total SCFA.    |
| Combined effects of oligofructose and <i>Bifidobacterium animalis</i> on gut microbiota and glycemia in obese rats (Bomhof <i>et al.</i> , 2014)   | Adult male SD mice were fed with high fat diet.                                 | Design: RCT intervention with 10% OFS, <i>B. animalis sub lactis</i> BB-12, and the combination of both for 8 weeks.<br>Analysis: extract of fecal bacterial DNA was analyzed by qPCR.            | F/B ratio decreased after administration of prebiotic (p=0.0015) and probiotic (p=0.0011). Prebiotics are able to lower the energy intake, increase body weight, and fat mass.                     |
| Yellow pea fiber improves glycemia and reduces <i>Clostridium leptum</i> in diet- induced obese rats (Eslinger <i>et al.</i> , 2014)   | Adult male SD mice were fed with high fat diet and sucrose.                     | Design: RCT intervention with oligofructose (OFS), yellow pea fiber (PF), yellow pea starch (PS), and yellow pea flour (PFL).<br>Analysis: extract of fecal bacterial DNA was analyzed by qPCR.   | <i>Firmicutes</i> and F/B ratio decreased in OFS, PF, and PFL groups. Pea fiber can lower the fasting blood glucose and the area under glucose curve.  |
| Apple-derived pectin modulates gut microbiota, improves gut barrier function, and attenuates metabolic endotoxemia in rats with diet-induced obesity (Jiang <i>et al.</i> , 2016)          | Adult male SD mice were fed with high fat diet.                                 | Design: RCT intervention with apple-derived pectin supplementation for 6 weeks.<br>Analysis: extract of fecal bacterial DNA was analyzed by qPCR.   | Administration of pectin can restore the abundance of <i>Bacteroidetes</i> and <i>Firmicutes</i> after high-fat diet induced. Moreover, it can also reduce inflammation and metabolic endotoxemia. |

lily bulbs (*Lilium leichtlinii* var. *maximowiczii* Baker) proves to be able to reduce the proportion of F/B ratio. Moreover, prebiotics and fiber contained in pea fiber (PF) and pea flour (PFL) can also alter the gut microbiota composition by reducing the *Firmicutes* level, namely *C. leptum* (Eslinger *et al.*, 2014), which usually increases in obese individuals (Angelakis *et al.*, 2012). Oligofructose is known to be able to elevate the abundance of *Bifidobacteria* which plays a role in intestinal health (Russell *et al.*, 2011). The research about oligofructose, prebiotics, and probiotics conducted by Bomhof *et al.* (2014) showed that oligofructose could increase the abundance of *Bifidobacterium spp.* and *Lactobacillus spp.*

Supplementation of lactic acid bacteria, such as *L. plantarum*, affects the reduction of adipose tissue accumulation and the changes in the gut microbiota (Park *et al.*, 2016). Despite not providing specific effect, the combination of probiotics and prebiotics are known to be able to decrease the F/B ratio. The decrease in this ratio is caused by the increasing number of *Bacteroides spp.* (Bomhof *et al.*, 2014). The prebiotic limitation

is the rapid fermentation process in the proximal colon. One of the prebiotics which can be fermented in stages is arabinoxylan (AX) since the structure relies on the enzyme spectrum. The effects of AX to the microbiota composition require six weeks, marked with the elevated levels of fecal SCFAs and the reduction of fecal pH (Grootaert *et al.*, 2009; Hughes *et al.*, 2007).

Studies of gut microbiota in the human gastrointestinal tract require invasive sampling methods that cannot be scaled for practical and ethical considerations. This is the reason why mice are often used as a better alternative for similar research. Mice have become the most studied models for microbial diversity in the gastrointestinal tract. The difference in the gastrointestinal tract between humans and mice, particularly in the tract size and dietary habits, can be the factors that differentiate the total size of the species in the gastrointestinal tract (Ley *et al.*, 2006; Rawls *et al.*, 2006). Nevertheless, the phylogenetic makeup of the microbiota composition in both humans and mice seems to share similarity at the phylum level, with

*Firmicutes* and *Bacteroidetes* as the two main bacterial phyla. Though the microbiota looks alike but the quantitative abundance is different (Krych *et al.*, 2013). This should be carefully considered during experimental design and interpretation.

To the best of our knowledge, this review was the first to attempt to discuss and elaborate on the effect of dietary factors in gut microbiota composition, especially in the *Firmicutes* and *Bacteroidetes* ratio.

The research articles in this review used standardized methods which could attribute to the accurate results. Though, most of the reviewed articles showed that there was a decrease in *Firmicutes* and an increase in *Bacteroidetes* in the effect of the dietary factors, yet the mechanisms of lowering the F/B ratio through the nutrients and bioactive compounds are still unclear. Future studies are required to discuss these mechanisms further. There were limitations from the research articles we reviewed, such as the studies did not observe and analyze further the modulation of dietary fiber on the gut microbiota composition; metagenomics method should be used to analyze and determine the gut microbiota composition; the unblended participants in data collection could be a possible factor for biases in psychological responses; and, there was a study conclusion that did not separate the gut microbiota in rats and humans which could not be attributed to translate the similar thing in humans. It is required to carry out clinical trials to address the benefits of apple-derived pectin in humans.

Also, there were several limitations to this review. This review did not separate the role and influence of dietary factors in human and animal studies and did not separate the obese and overweight subjects.

## CONCLUSIONS

The composition and ratio of the two microbiotas can be influenced by several factors, and one of them is nutrient dietary intake. Several nutrients, such as fiber, organic acid, polyphenol, and fat, can influence the alteration of the *Firmicutes* and *Bacteroidetes* composition. One of the ways suggested to reduce the number of obesity problems is by increasing the diet enriched with fiber, polyphenol compounds, organic acid,

fruits, and vegetables to make a better *Firmicutes* and *Bacteroidetes* composition.

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