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The Relationship of Mutualism Between the Diversity of Gut Bacteria Metabolism and The Human Body: A Review

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Abstract

Do you know the relationship of mutualism between the diversity of gut bacteria metabolism and the human body? Hearing bacteria our thinking is directed to something that pathogenic and parasitic to the host, not all bacteria can cause disease. Precisely the human body has a mutual relationship between gut bacteria and human metabolism such as helping in the digestive process of both coarse fiber, protein, fat, detoxifying toxins as well as endurance and maintaining homeostatic. The understanding of the mechanism of homeostatic gut bacteria is not fully known especially until the basic genetics and metabolism in each of these gut bacteria. This paper is expected to improve understanding of the interaction of intestinal bacteria such as Bacteroides, Bifidobacterium, Escherichia coli, Lactobacillus, and Saccharomyces boulardii to human metabolism, especially in detecting diseases and improving the health of the body. The focus of this paper is on the diversity of bacterial metabolic pathways in the human gut as well as the influence of the presence of such bacteria in the body. The studies was completed by study libraries with qualitative and quantitative data.

***Keywords**: Gut Bacteria Diversity; Metabolic Pathway; Mutualism; Human Body.*

Introduction

Microorganisms (archaea, bacteria, fungi, protozoa, microscopic algae and, viruses) can be found in all parts of the human body, especially on the outer surface of the skin, the inner surface of the digestive tract, oral mucosa and, conjunctiva. From the diversity of types of microorganisms, the number of bacteria is very much two to three times more than the number of other microorganisms. So that sometimes the mention of microbial cells in the human body is referred to as bacteria. Most of the bacteria are in the large intestine which is 1014 followed by the skin 1012 bacteria.

From the table, it is concluded that the largest number of bacteria is in the intestinal organs. So, it is necessary to know more about the metabolic processes carried out by intestinal bacteria. Broadly speaking, intestinal bacteria in the body have the ability to convert carbohydrates through a saccharolytic fermentation process or short-chain fatty acid / SCFA, which produces products such as acetic acid used by muscles, propionate acid helps the liver to produce ATP, and butyric acid provides cellular

energy. colon and can prevent cancer (Beaugerie et al., 2004). These products are used by host cells as the main source of energy and nutrition for humans, especially in the absorption of important minerals such as magnesium, calcium, and iron (Gibson and Glenn, 2004). Other evidence is that bacteria can increase the absorption and storage of lipids by facilitating the body to absorb the necessary vitamins such as vitamin K (Sears, 2005). Intestinal bacteria also synthesize vitamins (such as biotin and folate) and help the absorption of dietary elements (including magnesium, calcium, and iron) (O'Hara, 2006). With the ability of the intestinal bacteria above, there is a specific mutualism relationship in each species.

According to studies with a nucleic acid-based approach (targeting 16S rRNA), it shows that the normal gut flora consists of several major bacterial divisions, namely the phylum *Firmicutes* consisting of the genus *Ruminococcus, Clostridium, Lactobacillus,* and butyrate producers such as *Eubacterium, Faecalibacterium, and Roseburia*, Phylum *Bacteroidetes* consists of *Bacteroides*, *Prevotella,* and *Xylanibacter,* Phylum *Actinobacteria* includes the genus *Collinsella* and *Bifidobacterium* which make up 5-10% of the total intestinal bacteria, the phylum *Proteobacteria* consists of *Escherichia* and number of bacteria is in the intestinal organs. So, it is necessary to know more about the metabolic processes Desulvofibrio, Verrucomicrobia (Rajilic ´-Stojanovic´ et al. 2007; Eckburg et al. 2005; Eckburg et al.; Wang et al. 2005). So that in this paper five samples of bacterial metabolism are taken, namely Bacteroides, Bifidobacterium, Escherichia coli, Lactobacillus, and Saccharomyces boulardii.

Result and Discussion

Bacteroides

The first is *Bacteroides* because according to studies using a nucleic acid-based approach (targeting 16S rRNA) it has shown that diversity of bacterial species and identifying dominant bacterial groups, one of which is Bacteroidetes, make up 98% of the total microbiota in the gastrointestinal tract (Gillilland et al., 2012; Sekirov, et al., 2010; Cheng, et al., 2013). The proportion and composition of Bacteroidetes can consistently be stable in an individual. (Rajilic, et al., 2007; Eckburg, et al., 2005; Wang, et al., 2005). The characteristic of this bacteria is anaerobic, gram-negative, non-spore-forming, and rod-shaped bacteria. The amount of gastrointestinal microbiota when colonizing the human intestine is 5–8 × 1010 CFU / gram of feces (Zitomersky et al., 2011).

Bacteroidetes have a very large metabolic potential which is shown by their high flexibility to adapt to the nutritional conditions of the intestinal environment (Comstock and Coyne, 2003), for example being able to use food or glycans derived from the host according to nutrient availability (Sonnenburg et al., 2005). *Bacteroides* can also enter amino acids from outside (Smith and MacFarlane, 1998) which are all used to maintain cell structure and as a source of energy. *Bacteroides* get their food from the intake of host carbohydrates, especially in the form of oligosaccharides that the stomach or intestines can no longer digest (eg galactooligosaccharides and inulin). That way it can

support the growth of beneficial bacteria that it has the potential to improve gastrointestinal health (Mathers et al., 2009).

In addition, there is a mutualism relationship that occurs, for example, *Bacteroides* are involved in the digestion of certain foods that cannot be digested by the stomach and small intestine, so they can play a key role in maintaining energy homeostasis. In carbohydrate metabolism, *Bacteroides thetaiotaomicron* plays a role in the expression of the enzyme glycosyltransferases, glycoside hydrolases, polysaccharide lyases (Jandhalaya et al., 2015; Mathers et al., 2009) to catabolize fiber foods such as xyloglucans, which are usually found in vegetables (Larsbrink et al., 2014). These bacteria play a role in lipid metabolism by helping the efficiency of lipid hydrolysis by increasing the colipase expression required by pancreatic lipases to digest lipids. In protein metabolism, these bacteria play a role with human proteinases efficiently using microbial proteinases and peptidases. The bacterial cell wall contains amino acid transporters that can facilitate the entry of amino acids into the bacteria from the intestinal lumen (Jandhalaya et al., 2015; Mathers et al., 2009).

In addition, many of these bacterial metabolites are in suppression of colon cancer development; These include SCFAs (short-chain fatty acids) as the catabolic end products of the fermentation of intestinal bacteria of complex polysaccharides. The most abundant are acetate, propionate, and butyrate (Ríos-Covián et al., 2016a) which serve as an energy source for colonic epithelial cells (Howe et al., 1992; Clausen et al., 1991)

Several studies show Bacteroidetes as the largest propionate producer in the human gut (Salonen et al., 2014; Aguirre et al., 2016). Propionate influences lipid synthesis by hepatocytes. Lipid synthesis by the liver includes the conversion of food-derived fatty acids and glycerol to cholesterol and triglycerides with different fatty acid compositions. These hepatic lipid molecules are then incorporated into lipoproteins, for distribution to various tissues via circulation. This lowers the risk of cholesterol and hepatic lipogenesis. (Hosseini, 2011).

In an in vitro study of the cancer line, butyrate was found to exert tumor-suppressing effects by inducing apoptosis, inhibiting proliferation, inducing epigenetic changes, and modulating inflammatory matrix responses as well as cytokine levels. Hence, modulation of gut bacteria through diet control or antibiotic treatment. The manipulation of the gut microbiota to support and increase SCFA production through the use of prebiotic or indigestible foodstuffs may be a promising approach to the body's metabolic program, and may consequently affect cancer risk.

Among the SCFAs, propionate, in particular, has been studied as a satiety-inducing agent with strong effects on energy intake and eating behavior and this is associated with weight control. Bacterial regulation of intestinal peptides such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) is mediated by SCFA especially propionate. GLP-1 and PYY are satiety-stimulating hormones released in response to nutrient intake by L- cells, especially in the ileum and large intestine. GLP-1 increases insulin secretion and proliferation of pancreatic b-cells in addition to controlling glycogen synthesis in muscle cells, while PYY slows gastric emptying.

Escherichia coli

In second place is Escherichia coli, this bacterium is already familiar because of its role in human gut health, this bacteria is the first bacteria that exists in human digestion since the beginning of birth and paved the way for the formation of species of Bifidobacterium, Bacteroides and other genera (Mackie, RI, 1999). E. coli lives in large numbers in the human intestine, which is to help the human digestive system and protects against pathogenic bacteria. However, the new strain of E. coli is a dangerous pathogen that causes diarrheal disease (Damayanti, 2014). This happens when the number of bacteria in the digestive tract increases or is outside the intestine and produces enterotoxins that can cause diarrhea (Ningrum, 2012). Transmission of these bacteria through raw food and water, Undercooked and contaminated food, namely when food that has been cooked comes into contact with contaminated raw materials or equipment (Jawetz et al, 2005). Escherichia coli is used as an indicator of food quality. Escherichia coli is a Gram-negative bacterium, cocobacil with a size of 2.4 x 0.4 -0.7 µm, has petritic flagella so that it is motile, and cannot form spores (Jawetz et al., 2008). These bacteria are included in normal human flora but can cause serious diseases such as hemolytic uremic syndrome (HUS), hemorrhagic colitis (HC), food poisoning, and diarrhea (Hemeg, 2018). Escherichia coli is a Gram-negative bacterium, cocobacil with a size of 2.4 x 0.4 -0.7 µm, has petritic flagella so that it is motile, and cannot form spores (Jawetz et al., 2008). These bacteria are included in normal human flora but can cause serious diseases such as hemolytic uremic syndrome (HUS), hemorrhagic colitis (HC), food poisoning, and diarrhea (Hemeg, 2018). Escherichia coli is a Gram-negative bacterium, cocobacil with a size of 2.4 x 0.4 -0.7 µm, has petritic flagella so it is motile, and cannot form spores (Jawetz et al., 2008). These bacteria are included in normal human flora but can cause serious diseases such as hemolytic uremic syndrome (HUS), hemorrhagic colitis (HC), food poisoning, and diarrhea (Hemeg, 2018).

E. coli has several antigens, namely anti-gen O, H, and K, where the O (somatic) antigen which is the outermost part of the cell wall lipopolysaccharide and consists of repeating polysaccharide units, an O antigen is thermostable or heat resistant and alcohol (Hasibuan, 2016). H antigen (flagellum) is thermolabile or cannot withstand alcohol and heat at a temperature of 100oC. H antigen is maintained by giving formalin to mobile variants of bacteria such as Escherichia coli (Hendrayati, 2012), K antigen (capsule) consists of polysaccharides and is heat resistant and is present on the outside of bacteria, K antigen is outside of O antigen, K antigen. can interfere with agglutination through the O antiserum (Hasibuan, 2016).

Basic metabolic and physiological adaptations allow *E. coli* to replicate in a diverse host microenvironment. The extraintestinal pathogenic *E. coli*, which causes urinary tract infections, bacteremia, sepsis, and meningitis, have adapted to grow as a harmless commensal in the nutrient-rich and carbon-rich human intestine but is rapidly transitioning to a pathogenic lifestyle in nutrient-poor and nutrient-poor urinary tract rich in nitrogen. To establish commensal associations in the human gut, adaptive factors such as metabolic flexibility allow *E. coli* to successfully compete for carbon and energy sources with large and diverse bacterial populations. *E. coli* obtains nutrients from

intestinal mucus, including N-acetylglucosamine, sialic acid, glucosamine, gluconate, arabinose, fucose, and simple sugars that are released after breaking down polysaccharide complexes by anaerobic intestinal inhabitants. As UPEC transitions to the urinary tract, bacteria experience a drastic reduction in nutrient abundance and bacterial competition. Therefore, to replicate in the new host microenvironment, the utilization of UPEC metabolic pathways required for the growth of amino acids and peptides in the bladder signals bacteria to reproduce virulence properties to successfully cause invasive disease and survive the attack of bactericidal host defenses.

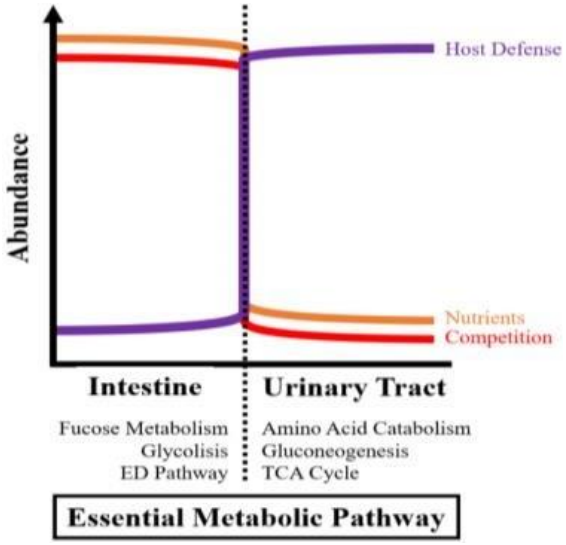

Figure 1. Adaptation factor

This adaptability is the unique and essential characteristic of ExPEC which enables successful transitions between different microenvironments in the same individual environment. Bacteria underwent a drastic reduction in nutrient abundance and bacterial competition. Therefore, to replicate in the new host microenvironment, the utilization of UPEC metabolic pathways required for the growth of amino acids and peptides in the bladder signals bacteria to reproduce virulence properties to successfully cause invasive disease and survive the attack of bactericidal host defenses. This adaptability is the unique and essential characteristic of ExPEC which enables successful transitions between different microenvironments in the same individual environment. Bacteria underwent a drastic reduction in nutrient abundance and bacterial competition. Therefore, to replicate in the new host microenvironment, the utilization of UPEC metabolic pathways required for the growth of amino acids and peptides in the bladder signals bacteria to reproduce virulence properties to successfully cause invasive disease and survive the attack of bactericidal host defenses. This adaptability is the unique and essential characteristic of ExPEC which enables successful transitions between different microenvironments in the same individual environment. Utilization of UPEC metabolic pathways required for the growth of amino acids and peptides in the bladder signals bacteria to reproduce virulence properties to successfully cause invasive disease and survive attacks by bactericidal host defenses.

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Escherichia coli is a health enhancer because it naturally colonizes the intestines of healthy mice and protects them from intestinal colonization and concurrent death by *Pseudomonas aeruginosa*. Reintroduction of fecal bacteria and *E. coli* in antibiotic-treated mice resulted in high *E. coli* titers in the host gut and increased defense against *P. aeruginosa* colonization and mortality. Surprisingly, high sugar concentrations supported the fermentation of *E. coli* to lactic and acetic acids and inhibited *P. aeruginosa* growth and virulence in aerobic culture and in aerobic models of metabolism in fats, when dietary plant fats-not carbohydrates or protein-supported fermentation and protects the host in it the intestines of anaerobic rats.

Bifidobacterium

The third place is Bifidobacterium, a genus of lactic acid bacteria that can be found in the large intestine of humans and animals. Bifidobacterium is a bacterium that is gram-positive, anaerobic, non-motile (immobile), does not form spores, is rod-shaped, and has a high percentage of G + C (guanosine-cytosine) (around 55-67%). Bifidobacterium cells usually form in pairs to form V or Y formations. Bifidobacterium experiences optimal growth at 37 to 41 ° C and a pH of around 6.5-7.

Sugar metabolism in the genus Bifidobacterium hexose is specifically degraded in the fructose-6- phosphate pathway. In its metabolism, fructose-6- phosphate phosphatase can be found, but there is no aldolase and glucose-dehydrogenase-6-phosphate.

The proportion of the final fermented products produced varies greatly from one strain to another. Small amounts of succinic acid are produced by some strains, and small amounts of CO2 can be produced during gluconate degradation.

The enzyme characteristic of sugar metabolism by the genus Bifidobacterium is fructose-6-phosphate phosphoketolase. The final fermentation product is formed by the sequential action of transaldolase, transketolase, xylulose-5-phosphate phosphoketolase, and enzymes belonging to the Embden-Meyerhoff-Parnas pathway, which act on glyceraldehyde-3-phosphate. Bifidobacterium can synthesize vitamins which include: thiamine (B1), riboflavin (B2), pyridoxine (B6), folic acid (B9), cyanocobalamin (B12), and nicotinic acid (PP). Five of these vitamins (except for riboflavin) were synthesized by most of the strains examined, and most of each (B6, B9, and B12) was excreted.

Bifidobacterial can survive in its host (large intestine). By combining membrane protein (MP), exopolysaccharide (EPS), TgaA, wall, and lipoteichoic acid (WTA and LTA)

then combined with sortase-dependent and Tad pili. *Bifidobacteria* degrade complex carbohydrates. The hydrolysis of complex sugars by certain Bifidobacterial species produces simple glycans which are directly utilized as a carbon source by the bifidobacterial species and for some other members of the genus Bifidobacteria, complex sugars are metabolized via cross-feeding.

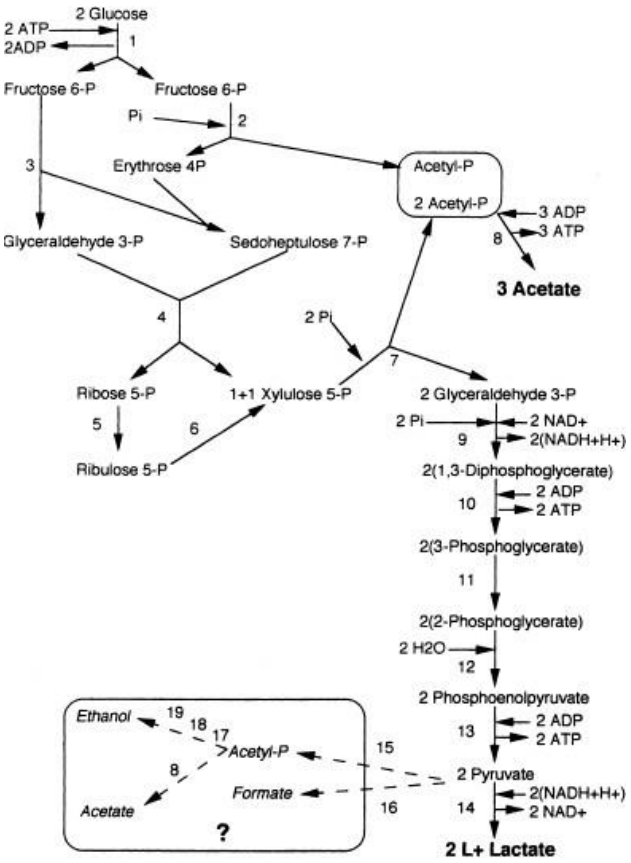

Figure 2. *Bifidobacterium* metabolism pathway

Lactobacillus

The fourth place is *Lactobacillus*. about 200 species are known to live in the human digestive tract. *Lactobacillus* can be easily found in the duodenum and ileum (Reuter G, 2001), but the number is very low in the colon (Hill GB, et al. 1984). In recent years, 50 species of *Lactobacillus* were found that could be detected in healthy human feces (Rossi M, et al. 2016). Based on the sugar fermentation pathway, *Lactobacillus* is included in: (1) homofermentative which only produces lactic acid through glycolysis; (2) facultative heterofermentative producing lactic and acetic acids via glycolysis or phosphorylase; (3) obligate heterofermentative which produces lactic and acetic acids, or ethanol via phosphorylase. *Lactobacillus* has similarities in hexose fermentation, which only breaks down the hexose phosphate with the glucose configuration. Glycolysis in homofermentative *Lactobacillus* is characterized by the breakdown of fructose 1,6-bisphosphate by aldolase into two triose phosphate groups which are then converted into lactate; thus glycolysis causes homolactic fermentation.

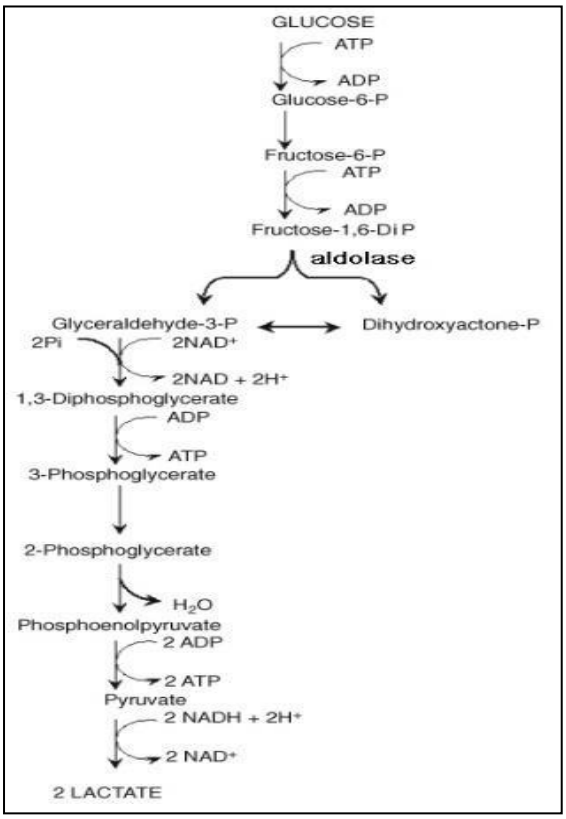

Figure 3. Homofermentation pathway in Lactobacillus. Source: Todar's Online Textbook of Bacteriology

In most of the *Lactobacillus*, lactose is transported by specific permease and broken down by β-galactosidase. However, in some *Lactobacillus* the lactose and galactose are taken up by the phosphoenolpyruvate (PEP) action system which depends on phosphotransferase. The formed lactose phosphate is hydrolyzed by P-β-galactosidase to produce glucose and D-galactose 6- phosphate. Glucose will then be processed through glycolysis and D-galactose 6-phosphate is processed through the D-tagatose 6-phosphate pathway (Kandler O, 1983).

The amount of *Lactobacillus* in the intestine will change when the body is attacked by diseases such as Crohn's disease, HIV, rheumatic arthritis, obesity, diabetes, irritable bowel, and prenatal stress (Dheeney D, et al. 2018). *Lactobacillus* in the intestine can survive bile acids by producing bile salt hydrolase (CBH) to catalyze the breakdown of the amino acid portion of the steroid nucleus from conjugated bile acids (Klaver et al. 1993). During lipid metabolism, micelle formation occurs, which helps the absorption of cholesterol in the intestine. Dietary fat emulsification is an intermediate step in fat absorption. *Lactobacillus* plays a role by de-conjugating bile salts in the intestine to form bile acids, thereby inhibiting micelle formation, decreasing cholesterol absorption.

Lactobacillus also produces bioactive peptides due to the fermentation activity of inactive ACE inhibiting peptides. Diets combined with *L. casei* have been shown to reduce hyperglycemia associated with insulin deficiency (Matsuzaki T, et al. 1997). Dysfunction of β pancreatic cells causes a decrease in insulin sensitivity in the regulation of blood glucose and fat metabolism (Boden G, et al. 2002), this is what causes diabetes.

In addition, it was found that obese children had less microbiota than thin children. This proves that the amount of microbiota in the gut is related to the development of obesity (Kalliomaki M, et al. 2008).

Lactobacillus is also known to be resistant to very low pH so that its function as a probiotic is not disturbed (Nishiyama K, et al. 2016). The results of *Lactobacillus* metabolism in the form of lactic acid and antioxidants (Liu YW, et al. 2011) are beneficial for humans because they can inhibit the growth of pathogenic organisms. Some *Lactobacillus* strains can immunomodulate human cells and trigger an anti-inflammatory response (Wang Y, et al. 2017).

Saccharomyces boulardii

Finally, *Saccharomyces boulardii* is a non-pathogenic yeast that is widely prescribed in the form of lyophilization in many countries and is used as a biotherapeutic agent [(McFarland LV, Bernasconi P (1993) and Elmer GW et al (1996)]. Although *S. boulardii* is a variety of S. cerevisiae, it differs from S. cerevisiae in several taxonomic, metabolic, and genetic traits [Hennequin C (2001) and Maillee M (2001)]. *S. boulardii* is resistant to acidity, to proteases, and naturally to all antibacterial antibiotics [Bergogne-Berezin E (1995) and Buts JP (1999)]. After oral administration of *S. boulardii*, stable concentrations of viable yeast cells were achieved in a mean time of 3 days and yeast was cleared from stool 2–5 days after discontinuation [Blehaut H (1989)]. The mechanism of action of *S. boulardii* includes a protective effect against various enteric pathogens and a beneficial effect on the intestinal mucosa of the host [Buts JP (1999)]. These bacteria can resist degradation by hydrolytic enzymes and bile salts.

The mutualism relationship carried out by these bacteria is that they can fight intestinal pathogens using a competition mechanism for nutrient consumption which results in limited nutrition for pathogenic organisms. having the ability to grow and colonize with metabolite production can lower intestinal pH which causes stress conditions for pathogens, reduce the adhesion of *Citrobacter rodentium* to epithelial cells by modulating virulence factors, can block toxin receptors or function as bait receptors for toxins, fight C. difficile infection by inhibition growth and decreased production of toxins due to secreted factors and stimulation of host mucosal disaccharidase activity, can inhibit the surface endotoxin of Escherichia coli through dephosphorylation, yields a 120-kDa protein that decreases chloride secretion stimulated by cholera toxin by reducing cAMP levels. *S. boulardii* is also able to attach to cholera toxin through its cell walls.

S. boulardii as an immunological function it acts as a pro-inflammatory stimulant or inhibitor. Especially in S. Typhimurium infection by reducing levels of pro-inflammatory molecules such as cytokine interleukin 8 (IL-8), mitogen-activated protein (MAP) kinase, and (nuclear factor kappa B) NF-kB signaling pathways.

S. boulardii as a modulator of required enzyme activity, such as stimulation of the digestive enzyme brush border membrane and nutrient transport activities such as iso-maltase activity; glucoamylase and N-aminopeptidase activity; brush border membrane

activity of sucrase, lactase, and maltase; levels of spermine, spermidine and putrescine in the jejunal mucosa of mice; leucine- aminopeptidase activity; Activity of α, α-trehalase in endoluminal fluid and intestinal mucosa; α-glucosidase brush limit; adenosine triphosphatase, γ-glutamyl transpeptidase, lipase, and trypsin activity and TNF-α, IL- 10, altering growth factor-beta (TGF-β), and secretory IgA; diamine oxidase activity, brush border sodium/glucose cotransporter 1 expression and sodium-dependent glucoseuptake.

S. boulardii as physiological and biochemical functions in various tissues help in rebuilding SCFA levels, which are suppressed during disease. Acetate and butyrate are major SCFAs in intestinal epithelial cells, which play a role in inhibitory function, anti-inflammatory, and immune-modulating pathways. One study reported that short-term (6 days) treatment with *S. boulardii* reduced the incidence of diarrhea in patients receiving nutrition by increasing levels of SCFA, especially butyrate. SCFA may also exhibit antimicrobial activity, and studies investigating several strains of *S. boulardii* and *S. cerevisiae* for their effectiveness in inhibiting E. coli, describe the exclusive production of acetic acid by *S. boulardii* as an antimicrobial mechanism. *S. boulardii* secretes nutrient transporters (sodium-glucose transport protein) which can be induced by its polyamine, as well as the activity of digestive enzymes (sucrase-isomaltase, maltase-glucoamylase, lactase-phlorizin hydrolase, alanine aminopeptidase, and alkaline phosphatase). These molecules are also able to protect lipids from oxidation and increase SCFA activity.

Conclusion

From the relationship between *Bacteroides*, Bifidobacterium, *Escherichia coli*, *Lactobacillus*, and *Saccharomyces boulardii* with the human intestine, it has a mutual relationship if the composition and proportion are balanced and stable. Each gut bacteria has a different metabolism. However, it can be underlined from the five gut bacteria discussed in this paper that it helps the digestive pathway and process in the intestine, both protein, fat, and fiber that cannot be digested by the human intestine. besides having a role in detoxifying toxins, fighting intestinal pathogenic bacteria as a form of body defense, and can maintain homeostasis. With this role, bacteria get nutrients for their survival.

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