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Edible Mushroom Potency to Alleviate Stunting Through Gut Microbiota Modulation: A Review

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ABSTRACT

Stunting has become a major concern in Indonesia since 30.8% of under-5-years old Indonesian children in 2018 suffer for it. Children who suffer from stunting have growth faltering and less intelligence capacity. In the long term, it will affect their adult life productivity and national human resources quality. Stunting represents a nutrient requirement for children are not achieved especially in 1000 first day of life. Despite a lot of various reason, lack nutrient intake and infectious disease are considered as the direct cause of stunting. Recent research has explored that microbe who cohabitate human intestinal can affect their host's health and nutritive status. The composition of gut microbiota is shown different between a healthy individual and stunted individual. Hence, there is a hypothesis that stunting can be alleviated by modulating the composition of gut microbiota. Various kind of edible mushroom can be found and has been part of the diet for several Indonesian. Not only mushroom contains high dietary fiber, vitamin, and mineral, but also several mushrooms are known for its immunomodulating effect. With plentiful prebiotic potential carbohydrates, like chitin, hemicellulose, β and α-glucans, mannans, xylans, and, galactans in mushroom, Mushrooms can act as prebiotics to modulate gut microbiota, and give health benefits to the host. This paper will present several shreds of evidence that edible mushroom has potency to become a source of prebiotic, affect gut microbiota composition, and prevent stunting. It also will show any obstacles in applying edible mushroom in an attempt of combating stunting, to give future research prospect in related studies.

Keywords: edible mushroom; gut microbiota; prebiotics; stunting

INTISARI

Stunting telah menjadi hal yang patut diperhatikan bagi Indonesia, karena 30,8% balita di Indonesia mengalami stunting pada 2018. Stunting menyebabkan pertumbuhan dan perkembangan, terutama kapasistas inteligensi, anak menjadi tidak optimal. Di kemudian hari, stunting akan memengaruhi produktivitas anak tersebut di masa dewasanya hingga kualitas sumber daya manusia nasional. Stunting menunjukkan tidak tercukupinya kebutuhan nutrisi anak terutama pada 1.000 hari pertama kehidupannya, yang dapat disebabkan oleh berbagai faktor. Asupan nutrisi yang tidak mencukupi dan terkena penyakit menular menjadi penyebab langsung seorang anak mengalami stunting. Penelitian terkini telah mempelajari bahwa mikroorganisme yang menghuni saluran pencernaan manusia dapat memengaruhi kesehatan tubuh manusianya itu sendiri. Kemudian, ditemukan perbedaan komposisi jenis-jenis mikroorganisme pada usus manusia yang sehat dan yang mengalami stunting. Sehingga, terdapat hipotesis bahwa stunting dapat ditanggulangi dengan mengubah komposisi mikrobiota usus. Di Indonesia, berbagai jenis jamur pangan telah umum dikonsumsi. Jamur pangan tidak hanya mengandung serat pangan, vitamin dan mineral yang tinggi, namun juga telah dikenal memiliki efek *immunomodulatory*. Jamur pagan juga mengandung berbagai jenis karbohidrat yang berpotensi memiliki aktifitas prebiotik, seperti kitin, hemiselulosa, β- dan α- glukan, manan, xylan, dan galaktan. Sehingga jamur pangan dapat berpotensi memodulasi mikrobiota usus dan memberikan efek kesehatan terhadap tubuh manusia. Artikel ini akan menunjukkan beberapa kajian potensi prebiotik dari jamur pangan, potensinya dalam mengubah komposisi mikrobiota usus dan menanggulangi stunting. Artikel ini juga akan tantangan dalam penggunaan jamur pangan untuk menanggulangi stunting untuk memberikan potensi penelitian lebih lanjut di bidang ini.

Kata kunci: jamur pangan; mikrobiota usus; prebiotik; stunting

INTRODUCTION

Stunting is defined as low-quality nutritive status in children. It is measured by calculating the z score from height divided by age, those who have z score lower than -2 is categorized as stunted. As a developing country, many children in Indonesia suffer from stunting. In 2018, according to the Indonesia Ministry of Health, almost one of the third children under 5 years old is stunted (30.8%) and considered as very high prevalence by WHO (Kemenkes RI, 2018). Stunting is not only responsible for the risk of child mortality but also forbids children to have their optimum cognitive and motoric development and makes them less excellent compared to non-stunted children as they grow up (Black *et al*., 2013; Romero-Velarde *et al*., 2017). This poor condition in Indonesia projecting the low quality of Indonesian human resources in the future, impacting national productivity, economy, and development. Thus, stunting problem in Indonesia is needs to be combatted.

Stunting appears as the sign of acute unfulfilled required nutrient for children, especially in the first 1000 days of life, which happens when they are in their mother's womb and days after they are born (approximately 270 and 730 days respectively). Directly, inadequate intake of calories and specific nutrients, such as essential amino acid, Fe, Zn, and vitamin A, and infection diseases become the main cause of stunting. These nutrients are needed as the precursor of protein synthesis which happens in the body of children, while infection disturbs nutrient absorption, and spends energy in overcome infection instead of for growth. However, several indirect causes of stunting also have impact to high prevalence of stunting in Indonesia, for instance, household food insecurity, poor parenting, and faulty health and environmental infrastructure (Torlesse *et al*., 2016; Beal *et al*., 2018;).

GUT MICROBIOTA AND ITS TRANSFORMATION DURING LIFE PHASE

Recent discovery finds out that human body is inhabited by numerous cells of microbes, which live in various body areas like skin, hair, reproduction tract, and gastrointestinal tract. The gut is inhabited by the densest population of various microbes, about 10^{14} cells or 10 times than their host cell itself. This population called gut microbiota has different composition in every individual and plays several roles in their host metabolism. Gut microbiota composition has symbiotic interaction with its host because it can degrade complex unabsorbed intakes into a simpler compound, make them easier to be absorbed, and at the same time, produce metabolites that might influence the condition of the host. In addition, diverse gut microbiota composition also restrains overgrowth of pathogenic microbes, and modulate the immune system (Shirajum Monira *et al*., 2011; Thursby & Juge, 2017). Intestinal is generally colonized by anaerobic bacteria, which belong into 3 group: Gram-negative Bacteroidetes, Gram-positive Firmicutes, and Actinobacteria. Enam puluh (60) % of total population of intestinal microbiota is Firmicutes phylum, while Bacteroidetes cover around 10% and Actinobacteria are around 30% (Arumugam *et al*., 2011; Borewicz *et al*., 2020). However, the composition of gut microbiota is dynamically shifted depending on age, diet, and gut environment, including pH, oxygen, nutrient, and temperature (Arumugam *et al*., 2011; Ursell *et al*., 2012).

Gut microbiota colonization starts before an individual is born. During pregnancy, vertical transmission of gut microbiota happens from mother to fetus (Martín *et al*., 2003). The colonization resumes during laboring and lactating. Natural method of delivery in laboring (through vagina) makes baby is exposed to reproductory tract microbiota, while it is not happening in c-section method of delivery. Later on, during lactating period, baby may only consume breast milk or formulated milk, milk from animal which is formulated to imitating the nutrition of human milk. Breast milk naturally contains prebiotic, an ingredient which cannot be absorbed by body but can be utilized by gut microbiota, called Human Milk Oligosaccharide (HMO) (Borewicz *et al*.,

2020). It promotes the growth of beneficial bacteria *Bifidobacterium* spp. especially *Bifidobacterium longum*. Gut microbiota composition of baby is dominated by Proteobacteria and Actinobacteria, then the population of Firmicutes and Bacteroidetes is increasing gradually as the age (Arumugam *et al*., 2011; Bäckhed, 2011; Eckburg *et al*., 2005). In the weaning period, baby starts to consume complementary food. This food complements the intake of human milk since it does not fulfill calories required by baby anymore. Complementary food also prepares baby intestinal tract before they consume family food. During this stage, the population of *Bacteroides*, *Eubacterium*, anaerobic *Streptococcus*, and *Clostridium* rises, on the contrary, *Bifidobacterium* population decrease 10% from total population (Mitsuoka, 1992). Thus, their composition starts to be similar to adult gut microbiota composition. Diet and lifestyle become the most influencing factor in gut microbiota composition modulation (Rodríguez *et al*., 2015).

The pattern of diet deciding gut microbiota composition and has been used to classified several types of gut microbiota composition, called enterotype. According to Nakayama *et al* (2015), there are 2 types of entrepreneurs in Asia (represented by Indonesia, Thailand, China, Japan, and Taiwan). Prevotella enterotype (P-type), which is very related to high consumption of carbohydrates, can be found in Indonesian (Yogyakarta and Bali), and Thai (Khon Kaen). Meanwhile, *Bifidobacterium*/ *Bacteroides* enterotype (BB-type) is related to animal-based protein consumption. BB-Type can be found in Thai (Bangkok), Chinese (Beijing and Lanzhou), Japanese (Tokyo and Fukuoka), and Taiwanese (Taipei and Taichung). Usually, nutrients such as carbohydrates and protein will be digested and absorbed by the human upper intestinal tract, only undigested complex compounds that will reach the colon and become substrate for the growth of gut microbiota. *Prevotella* can metabolize fiber such as cellulose and xylan, therefore it is abundant in high carbohydrate consumers. *Bacteroides*, even though has the ability to utilize glycan, are able to degrade animal sources of glycoproteins and make them abundant in high animal protein consumers (Wu *et al*., 2011).

Not only regulates gut microbiota composition, but diet also regulates metabolite produced by each microbe in gut especially Short-Chain Fatty Acid (SCFA) for example acetate, propionate, and butyrate acid. Each microbe has its metabolism in producing these SCFA, depends on the kind of substrate and environmental condition. For instance, Phylum Firmicutes is able to produce butyrate acid, which is beneficial as anti-inflammatory and anti-cancer. While there is significant correlation between the number of phylum Bacteroidetes and propionate acid in the colon (Flint *et al*., 2012).

GUT MICROBIOTA COMPOSITION OF STUNTING AND UNDERNUTRITION CHILDREN

The deficiencies of both macronutrients and micronutrients are not the leading causes of undernutrition. The emerging researches provide evidence that the gut microbiota has a significant role in regulating host metabolism. It may happen because certain gut microbiota compositions may decide whether it will assist or in contrast, disturb nutrient digestion and absorption. Dysbiosis, is an imbalance of gut microbiota composition and is observed in undernutrition children. The association of gut microbiota composition and undernutrition is a vicious cycle (Figure 1) (Relman, 2013). The gut microbiota perturbation in undernutrition children, characterized by low bacteria diversity, delayed gut microbiota maturity, and high occurrence of potentially pathogenic bacteria, provokes the epithelium impairment or Environmental Enteric Dysfunction (EED) (Velly *et al*., 2017).

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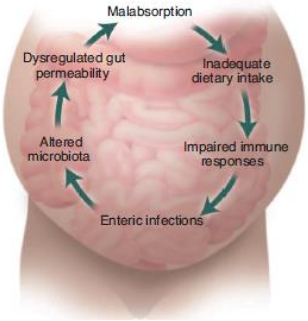

Figure 1. Vicious cycle of undernutrition (Relman, 2013)

EED is a pathology of intestinal indicated by mucosal atrophy, villous blunting, crypt branching, and epithelium inflammation (Thaxton *et al*., 2018; Singh *et al*., 2020). The gastrointestinal tract has two primary functions, one is as a facility for macromolecule degradation by secreting enzymes and nutrition absorption for energy. The other function is as an immune system against pathogen microorganism infection. The impairment of epithelium leads to nutrient malabsorption and hence faltering the children's growth. It is also increasing the oxygen level in lumen and promoting the growth of aerotolerant such as Enterobacteriaceae.

Gut environment is normally anaerobic, which promotes the growth of beneficial obligate anaerobe bacteria to produce SCFA by fermenting indigestible carbohydrates. The domination of facultative anaerobe bacteria, known as dysbiosis, indicates that there is a disruption in gut integrity of undernutrition children. The colonic epithelium is continually renewed, and PPARγ (peroxisome proliferator-activated receptor gamma) is needed for terminal cell differentiation. Butyric acid activates this receptor for fatty acid metabolism through β-oxidation of long-chain and short-chain fatty acid. This pathway requires high oxygen consumption and therefore resulting in a low level of oxygen in lumen, known as epithelial hypoxia (Litvak *et al*., 2018). In contrast, epithelium inflammation shifts the terminally differentiated colonocytes toward anaerobic glycolysis, characterized by low oxygen consumption, high glucose consumption, and high lactate release. As a result, the epithelial hypoxia is disrupted and elevates the amount of diffused oxygen from mucosal surface to the lumen, followed by the expansion of facultative anerobic bacteria. Additionally, the depletion of SCFA due to domination of facultative anaerobe bacteria, elevates the synthesis of iNOS, an enzyme that contributes to the generation of nitric oxide (NO), which is further can be converted into nitrate (NO_3^-) that acts as electron acceptors for facultative anaerobe bacteria (Litvak *et al*., 2018).

Table 1. Recent researches regarding gut microbiota in undernutrition children

Location	Age	N	Finding	Reference
Bangladesh	2-3 yo	Normal: 7 Undernutrition:7	High relative abundance of Proteobacteria and low Bacteroidetes in undernutrition group. Specific genus identified in undernutrition: *Klebsiella* and *Escherichia*	(Shirajum Monira *et al*., 2011)
India	5-60 mo	20 children with varying nutritional status	Identified genus in malnutrition: *Escherichia*, *Streptococcus*, *Shigella*, *Enterobacter* dan *Veillonella*	(Ghosh *et al*., 2014)
Senegal and Niger	13-25 mo	Normal: 5 Severe malnutrition: 10	High number of Proteobacteria and *Streptococcus gallolyticus* in severe malnutrition	(Alou *et al*., 2017)
Indonesia	± 40 mo	Normal: 15	High relative abundance of Proteobacteria and low Bacteroidetes in undernutrition group.	(Kamil *et al*., 2021)

		Moderate undernutrition: 13	Identified biomarker in undernutrition: *Methanobrevibacter, Anaerococcus, Eubacterium*, and *Succinivibrio* No significance difference in diversity index	
Indonesia	± 48 mo	Normal: 53 Stunting: 78	Low abundance of Bacteroidetes in stunted Low abundance of *Prevotella_9*	(Surono *et al*., 2021)

Attempts to identified gut microbiota composition as a signature in undernutrition children have been conducted (Table 1). The infectious enteric bacteria are commonly identified. Despite the low bacterial richness, overrepresent of Proteobacteria phylum and its genera such as *Enterobacter, Escherichia, Klebsiella*, and *Shigella,* is observed in undernutrition children (Shirajum Monira *et al*., 2011; Ghosh *et al*., 2014; Alou *et al*., 2017; Kamil *et al*., 2021; Surono *et al*., 2021). The domination of *Proteobacteria* is followed by the depletion of Bacteroidetes phylum. The low number of Bacteroidetes phylum cause the deficiency in N-glycan pathway which contributes in the efficiency of energvy extraction from indigestible polysaccharide (Flint *et al*., 2012). The same result is reported in moderate undernutrition children living in Yogyakarta, Indonesia, even though no significant difference in bacterial diversity compared to the normal children. Beneficial bacteria that help producing SCFA such as *Bifidobacterium, Butyrivibrio, Faecalibacterium, Lactobacillus,* and *Roseburia* found to be depleted in undernutrition children (Fluitman *et al*., 2017; Velly *et al*., 2017). In addition, the number of *Akkermansia*, a biomarker genus of gut health conditions is low (Kamil *et al.*, 2021). *Akkermanisa* is mucosa colonizing bacteria, which degrade the mucosa for their carbon sources to produce SCFA (Reid *et al*., 2011). The ability of this genus to colonize on the surface of epithelium, are able to inhibit the invasion of pathogen (Derrien *et al*., 2011).

Dysbiosis, gut microbiota imbalance with domination of potentially pathogenic bacteria, has been reported in several incidences of undernutrition. Therefore, gut microbiota modulation is suggested to conquer the imbalance of gut microbiota. The main target of gut microbiota modulation is to promote the growth of beneficial producing SCFA bacteria. Notably, children who suffered severe acute malnutrition (SAM), possess low SCFA containing in their fecal sample, mainly propionic and butyric acid (Monira *et al*., 2010; Pekmez *et al*., 2018). The three dominants SCFA detected in human intestine are acetic, propionic, and butyric acid, which have molar ratio 3:1:1. SCFA, a metabolite produced by fermenting indigestible polysaccharide, is assumed to regulate the host metabolism through several mechanisms, even though it remains unclear.

On the surface of gut epithelial was deposited by several receptors, which may be regulated by the presence of SCFA. Free fatty acid receptor or G-protein coupled cell (GPR) 41 and 43 are the kind of SCFA dependent receptors, which not only deposited on the gut epithelial but also human white adipose tissue, skeletal muscle, and liver. It indicates that SCFA might also regulate substrate and host energy metabolism in peripheral tissue through endocrine response modulation, enzyme activity and transcription factors (Canfora *et al*., 2015; Li, Shimizu, & Kimura, 2017). The improvement of gut integrity by SCFA activated GPR41/43 through reducing the activity of histone deacetylases (HDACs), is one of the possible improvement mechanisms in undernutrition. HDACs is an enzyme contribute in epithelium inflammation. Inhibition of HDACs by butyric acid consequently prevents the over production of proinflammatory signals (Ratajczak *et al*., 2019). Additionally, butyric acid stimulates the PPRɣ to maintain the hypoxia state of lumen through oxidative phosphorylation (Litvak *et al*., 2018). Not only by stimulating several receptors, SCFA also leads lumen acidification, which is unfavorable for pathogen growth. The low lumen pH generates acidification of pathogen's cytoplasm and disturbs pathogen

transport electron by hinder the electron receptor (O_2 and NO_3) (Litvak *et al*., 2018). Other than that, acid condition of gut environment helps adsorption of several minerals such as Fe, Ca, and Zn (Scholz-Ahrens *et al*., 2007).

SCFA also improves the efficiency of host energy metabolism (Fluitman *et al*., 2017). Glucose is the main carbon source for energy generation, which can be provided by gluconeogenesis. Gluconeogenesis not only occurs in the liver, but also in kidney and intestine, characterized by the activity of glucose 6-phosphatase. At the low enteral intake (fasting or malnutrition), the intestinal gluconeogenesis activity is improved from 5-7% in normal state to 20%. SCFA acts as a substrate for intestinal gluconeogenesis, in which almost 70% of energy for epithelium is provided by oxidation of butyric acid (Soty *et al*., 2017). Consequently, it helps to elevate the blood glucose and insulin sensitivity, and hence optimal energy generation. The improvement of insulin sensitivity is due to activation of AMP activated protein kinase (AMPK) in liver and muscle by butyric acid, which improves the uptake of blood glucose for energy generation (Canfora *et al*., 2015).

Furthermore, adipogenesis, a metabolism generating adipose tissue which consists of determination and differentiation steps, is also upregulated by SCFA (Yan & Ajuwon, 2015). Determination steps are precursor generation which preadipocytes, while differentiation is the development preadipocytes to adipose tissue. The role of SCFA mainly propionic and butyric acid in adipogenesis takes place during differentiation by activating several receptors, such as PPRɣ, C/EBPα, and C/EBPβ. Butyric acid also prevents lipolysis and peroxisome oxidation. Moreover, propionic acid elevates Fatty Acid Synthase (FAS) activity.

GUT MICROBIOTA MODULATION AS STUNTING AND UNDERNUTRITION ALLEVIATING STRATEGY

The means of modulating gut microbiota composition can be executed by three proposed treatments, which are antibiotic, probiotic, and prebiotic (Velly *et al*., 2017). Antibiotic is commonly used as a treatment of pathogen invasion. However, emerging research indicates that antibiotic may have adverse effects such as reducing bacterial diversity, shifting in metabolic activity, and initiating antibiotic-resistant bacteria which leads to the antibiotic-associated diarrhea (Ramirez *et al*., 2020). The use of probiotic, prebiotic or their combination is promising to modulate gut microbiota, since there are no serious negative effects reported. Though, the evidence of how far they can modulate is lacking. Several researches reported that administering probiotic, prebiotic and their combination improves nutritional status of undernutrition children, even though the gut microbiota composition is not analyzed (Table 2).

Administering mix probiotic *L. rhamnosus* GG and *B. animalis* subsp. lactis BB-12 to undernutrition children in Uganda modulates the gut microbiota domination from *Klebisella* and Enterobacteriaceae to *L. ruminis*, *Blautia spp*., and *Faecalibacterium prausnitzii* (Castro-Mejía *et al*., 2020). Randomized double blind control trail research conducting in Yogyakarta, Indonesia, indicates that administering *L. plantarum* Dad-13 supplemented in jelly candy can promote the growth of beneficial bacteria such as *Collinsella*, *Catenibacterium*, *Faecalibacterium*, and *Subdoligranulum*, which are known as butyric acid producer (Kamil, 2021). Therefore, treatment by administering probiotics and prebiotic may be implemented as a way to modulate gut microbiota composition.

Table 2. Gut microbiota modulation intervention in stunting and undernutrition studies

Age (yo)	Location	N	Treatment	Duration	Output	Reference
1-3	India	I: 312 C: 312	I: *Bifidobacterium lactis* HN019 1.9x10^{7}CFU/d +2,9 g/d prebiotic incorporated into milk powder C: milk powder	1 year	Improvement of body weight, body height, WAZ and HAZ	(Sazawal *et al*., 2010)
2-5	India	I: 50 C: 50	I: *L. acidophilus* 10^8 CFU/g in curd juice beet C: isocaloric supplement (biscuit)	6 months	Improvement of body weight and body height	(Saran *et al*., 2002)
3-5	China	I: 201 C: 201	I: *S. thermophiles, L. bulgaricus* and *Bifidobacterium* incorporated into yoghurt C: normal diet	9 months	Improvement of WAZ and HAZ	(He *et al*., 2005)
2-5	Indonesia	I: 30 C: 40	I*: Enterococcus faecium* IS-27526 (2,31x10^8 CFU/d) incorporated into UHT milk C: maltodextrin incorporated into UHT milk	90 days	• Improvement of body weight • Increment of sIgA	(Surono *et al*., 2011)
10-12	Indonesia	I: 20 C: 20	I: *L. plantarum* Dad-13 (1,18 × 10^9 CFU/g) powder C: skim milk powder	60 days	• Improvement of BMI • Elevation of fecal SCFA	(Mustangin, 2018)
3-5	Indonesia	I: 15 C: 15	I: Jelly candy *L. plantarum* Dad-13 (10^8 CFU/g) C:	50 days	• Improvement of body weight, body height WHZ, WAZ, and HAZ • Elevation of fecal SCFA	(Kamil, 2021)

I: intervention; C: control

POTENCY OF EDIBLE MUSHROOM FOR STUNTING AND UNDERNUTRITION

Various kind of edible mushroom has been locally cultivated and widely consumed in Indonesia, such as white oyster mushroom (*Pleurotus ostreatus*), straw mushroom (*Volvariella volvacea*), white button mushroom (*Agaricus bisporus*) and ear wood mushroom (*Auricularia auricula*). Some imported edible mushrooms, for example, portobello mushroom, enoki mushroom (*Flammulina velutipes*), and shiitake mushroom (*Lentinula edodes*) are also getting popular as regular diet in Indonesia. These mushrooms are not only being consumed for their delicacy, but also for their nutritional and health benefit which they contain. Mushrooms contain a relatively high amount of protein, mineral, vitamin, and dietary fiber. They also contain immunomodulatory agents, antioxidant compounds, and prebiotic properties (Ho *et al*., 2020; Valverde *et al*., 2015). Thus, edible mushroom has potency for combating stunting.

Protein content of mushroom varied from 16.47-36.96 % (db) depends on the type of mushroom. Compared to protein content of beef jerky (33.20% db) and whole milk (26.32% db), mushroom can alternatively be a more affordable source of protein. They also contain a relatively high amount of essential amino acid especially tryptophan, methionine,

and threonine. Several mushroom Champignon (*A. bisporus*), Portobello (*A. bisporus*), shiitake (*L. edodes*), pink oyster (*P. djamor*), and white oyster (*P. ostreatus*) meet esensial amino acid score standard from FAO, therefore they can be classified as a good source of essential amino acid (Bach *et al*., 2017; González *et al*., 2020). Protein and amino acids are needed by infants especially for their growth, as they play an important role as building blocks of body tissue, and in metabolism. Essential amino acids even become one of the main defining factors of stunting in children, as it is found relatively lower essential amino acids in stunted individuals compared to the healthy (Semba *et al*., 2016).

Mushroom is also rich in riboflavin (B2 vitamin) and niacin (B3 vitamin), also moderately high in folate (vitamin B9) (Mattila *et al*., 2001). Mushroom also is the only source of non-animal based vitamin D (Valverde *et al*., 2015). Those vitamins are needed for the growth of children. Riboflavin and niacin play role in energy-producing metabolism. Then folate involves in protein metabolism, red blood cell production, and is critical in fetal development. While vitamin D role mainly in calcium metabolism especially in bone structure (Gibney *et al*., 2009). Representing mineral content in mushroom, ash content of mushroom varied from 6.93 to 11.85 % dry matter, which mostly potassium, phosphorus, magnesium, calcium, copper, iron, and zinc (Valverde *et al*., 2015; Bach *et al*., 2017). Potassium (K) is critical for nerve transmission and muscle function. Additionally, K play part in energy metabolism and cell growth. Phosphorus (P) is a major component of most biological membranes including body tissue during children growth. Magnesium (Mg) is important in various fundamental cellular reactions, from energy-yielding metabolism to protein synthesis. Calcium (Ca) is required for the growth of the skeleton. Copper (Cu) is a component of a lot of enzymes, cofactors, and proteins in human body. Iron (Fe) is present in hemoglobin, part of red blood cells, hence it is required in oxygen transportation and cell respiration. Zinc (Zn) has wide function of catalytic, structural, and regulation in human body, especially in immune system development (Gibney *et al*., 2009). Chronic deficiency of Fe and Zn is closely correlating with stunting (Kusudaryati, 2013).

Immunomodulatory properties of edible mushroom have been studied intensively for hundred years before. Multiple immunomodulatory compounds have been explored in various edible mushroom and their immunomodulatory mechanism of action also has been elucidated. One of the most studied immunomodulatory compounds is β-glucan which has different structures depends on their species. Lentinan, specific β-glucan from shiitake (*L. edodes*), schizophyllan from splitgill (*Schizophyllum commune*) and pleuran from white oyster (*P. ostreatus*). Lectin, a specific protein which conjugate with certain polysaccharide, also carry immunomodulatory properties and can be found in various edible mushrooms such as white button, enoki, yellow oyster (*P. citrinopileatus*), splitgill, and straw mushroom. Some Fungal Immunomodulatory Protein (FIP) can also be found in enoki and straw mushroom. The other immunomodulatory compound is terpenes and terpenoid which can be found in enoki and king oyster mushroom (*P. eryngii*) (Valverde *et al*., 2015; Zhao *et al*., 2020). These immunomodulatory compounds in edible mushroom may help children against infectious disease, especially gastroenteritis which can lead to growth faltering and stunting (Torlesse *et al*., 2016).

Edible mushroom contains numerous antioxidant compounds, such as phenolics, flavonoids, glycosides, polysaccharides, tocopherols, ergothioneine, carotenoids, and ascorbic acid. They can be extracted from fruiting body, mycelium, and growth media of edible mushroom. Additionally, mushroom is also rich in Zn, Cu, and Fe minerals which are cofactors of enzymes with antioxidant functions (Kozarski *et al*., 2015). Antioxidant properties in ear wood mushroom also has been studied by Elfirta and Saskiawan (2020). Antioxidant properties of mushroom may inhibit the generation of Reactive Oxygen

Species (ROS) who leads to oxidative stress. ROS may oxidize cellular component in children body and causes cell damage and loss function. This condition will lead to growth impairment, immune maturation, and neurodevelopment impairment (de Heredia *et al*., 2015).

ROLE OF EDIBLE MUSHROOM AS PREBIOTIC INGREDIENT TO MODULATE GUT MICROBIOTA COMPOSITION

Prebiotic is defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit", thus prebiotic has been used as evolving strategy in improving human health through microbiota modulation, especially in gastrointestinal. In human gastrointestinal tract, prebiotic must fulfill some requirements, that is it must be undigested by human upper digestive tract, can only be utilized specifically by beneficial microbiota and not by harmful microbiota, can be fermented by beneficial microbiota, and produce beneficial fermentative by-product (Wang, 2009; Gibson *et al*., 2017). FOS, GOS, and inulin are the most studied prebiotic ingredient. However, mushroom has a potency of prebiotic substance that can be explored furthermore. Mushroom cell wall is made of β-glucan polysaccharides, a homopolymer of glucoses which are bounded by 1,3 or 1,6 glycosidic bound. This β-bound is unable to be digested by mammalian pancreas secreted digestive enzymes, hence it may accommodate one of prebiotic criteria (Aida *et al*., 2009; Jayachandran *et al*., 2017; Van Loo, 2012). Moreover, mushroom also contains various polyphenol compound, since polyphenol has been intensively studied and projected to be new candidate of prebiotic substance (Gibson *et al*., 2017; Cardoso *et al*., 2021). In vitro studies of mushroom prebiotic activity are conducted by extracting fruiting body of mushroom. Then they supplement the extract to growth media of probiotic or fecal microbiota and detect the promotive growth of beneficial bacteria and the restrictive growth of harmful bacteria during fermentation. They also detect the SCFA of media after incubation to observe the beneficial fermentative by-product as one of the prebiotic criteria requirements. On the other hand, mushroom prebiotic activity in in vivo studies, mushroom is supplemented as diet of experiment animal. After several days of experiment, the prebiotic activity is observed from their feces or cecal after undergoing abdominal cavity opening. The study of prebiotic activity from various edible mushroom is shown in Table 3.

Table 3. Edible mushroom prebiotic activity studies

Research scale	Treatment	Mushroom used	Output	Reference
In vitro	Supplementation various mushrooms extract in *L. acidophilus* and *L. plantarum*	*A. auricula-judae, L. edodoes, P. citrinopileatus, P. djamor, P ostreatus, P. ostreatus (Jacq.Fr.) Kummer and P. pulmonarius*	Different kind of probiotic and mushroom possess different symbiotic effect	Sawangman *et al*. (2018)
In vitro	Observing prebiotic properties of mushroom extract on *L. acidophilus*	Various wild mushroom	Certain wild mushroom extract has prebiotic properties compared to commercial prebiotic (FOS and Inulin)	Nowak *et al*. (2018)
In vitro	Observing prebiotic properties of β-glucan of various mushroom on fecal batch culture	*S. commune* Fr (Splitgill mushroom) and *A. auricula* Judae	β-glucan of *A. auricula* Judae specifically enhancing growth of beneficial bacteria while β-glucan *S. commune* Fr inducing SCFA production	Chaikliang *et al*. (2015)

		(ear-wood mushroom)		
In vivo	Supplementation β-glucan from mushroom and *L. fermentum* JS KCCM 10499 in feed	*Sparassis* sp. (Cauliflower mushroom)	Synbiotic supplementation has decrease Proteobacteria and Firmicutes: Bacteroidetes ratio	Jeong *et al.* (2017)
In vivo	Supplementation mushroom heteropolysaccharide in feed	*Grifola frondose* (Maitake mushroom)	Increase *Allobaculum, Bacteroides,* and *Bifidobacterium.* Decrease *Acetatifactor, Alistipes, Flavonifractor, Paraprevotella, and Oscillibacter.*	Li *et al.* (2019)

FURTHER RESEARCH PERSPECTIVE

Though mushroom contains a lot of nutrition, mushroom need to be combined with another food ingredient if it going to be used as diet for children. Setyawan *et al.*, (2021) have develop a complementary food product by using white oyster mushroom and compare its nutritional characteristic to recommended daily intakes of infant. However, the high amount of dietary fiber content in mushroom becomes a backfire, since infant is unable to consume to much dietary fiber due to its lack of energy density and potentially causes flatulence in infant. A better formulation is needed to optimize the promising strategy to apply mushroom for stunting and undernutrition. A polyphenol-based prebiotic compound from mushroom can be further promising research field, since most studies are focus on β-glucan, which also can be classified as dietary fiber, as prebiotic ingredients. Additionally, more clinical trial also needs to be conducted to examine and proof that this edible mushroom and gut microbiota modulation is a good strategy to overcome stunting and undernutrition in children.

CONCLUSION

Stunting and undernutrition have become problem in Indonesia, and it can get more complicated and damaging in the future if it is not coped. Studies have shown the correlation between gut microbiota composition and nutritive status of human, including in stunting and undernutrition. Therefore, hypothetically stunting and undernutrition can be treated by aiming at the gut microbiota of children. Edible mushroom not only contains a lot of nutrition and bioactive compounds that promotes the overall health and growth of children, but also contain prebiotic ingredients such as β-glucan and polyphenol. This edible mushroom carries potency in becoming stunting alleviating agent. However, more study is needed to be conducted to apply edible mushroom to stunting and undernutrition, such as food product formulation, and clinical trials.

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CONTRIBUTORSHIP

RHS contributes in designing the manuscript, discussing edible mushroom potency, and editing and finalizing the manuscript. While RZK contributes in discussing gut microbiota and stunting. RHS and RZK are equally the main contributors in this manuscript.

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