

Review Article

Nutrigenomic and Biomolecular Aspect of *Moringa oleifera* Leaf Powder as Supplementation for Stunting Children

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ABSTRACT

Stunting is a global health problem. Based on WHO data, there are 161 million children who experience stunting. Breastmilk supplementation in the form of *Moringa oleifera* leaves powder is known to be beneficial in suppressing the stunting incidence. *Moringa oleifera* leaves powder contains protein, micronutrients, and minerals such as calcium, iron, sodium, vitamins C and E, beta carotene, and antioxidants (flavonoid acids, phenolic acids, glucosinolates, isothiocyanates, and saponins). The use of *Moringa oleifera* leaves powder in stunting cases has been carried out, but further studies in the aspects of nutrigenomics and molecular biology have not been conducted. This study is a literature review of relevant articles from www.pubmed.com, www.sciencedirect.com, and scholar.google.com. The author used keywords "stunting", "nutrigenomics", "biomolecular", and "*Moringa oleifera*". Pathogenic microbe such as *Shigella* and pathogenic *E. coli* ingestion can cause changes in DNA sequences in the stunting pathogenesis. *Moringa oleifera* leaf powder can pass through nutrigenomic and biomolecular mechanisms. Some macro and micromolecules of *Moringa oleifera* leaves powder such as folate plays a role in DNA methylation; vegetable protein and fatty acids act as promoters in DNA sequences; vitamins act as cofactors for enzymes, antioxidant, and antiinflammation. Seeing various potential mechanisms in the aspects of nutrigenomic and molecular biology, *Moringa oleifera* leaves powder can be used in overcoming stunting. Further research is needed to give more review about cytokines and molecules included in this literature review.

Keywords: biomolecular, *Moringa oleifera*, nutrigenomic, stunting

INTRODUCTION

Stunting is a chronic nutritional deficiency problem that starts at early development which causes growth retardation thus the children will be shorter than it should be based on their age development ([De Onis & Branca 2016](#)). In addition to physical suffering, stunting also causes cognitive growth disorders ([Zhang & Chandola 2017](#)).

Stunting remains a global health problem to date. Based on the WHO data, there are 161 million stunted children worldwide ([World Health Organization 2015](#)). Indonesia is the fifth country with the most stunting

cases as many as 26% in 2015 which affected children under five years old ([Kemenkes 2013](#); [Kemenkes 2018](#)).

When stunting is not addressed properly, it will become a serious problem for the government because it relates to the nation's future human resources. The Indonesian government has launched nutritional interventions that improve public education and specific supplementary nutrition. Specific nutritional intervention is done by providing complementary foods of breastmilk ([Mitra 2015](#)).

Giving the right complementary foods is known to be effective in suppressing the incidence of stunting. Food that can be given as complementary foods is *Moringa oleifera* leaves powder ([Kuswanto & Widanti 2018](#)). *Moringa oleifera* or Moringa plants are abundant in Indonesia ([Dhakar et al. 2011](#)). *Moringa oleifera* is a commodity that is widely grown in Indonesia which is potentially used as economically cheap complementary foods. The use of *Moringa oleifera* leaves has been carried out in a number of communities. For example, a study conducted in Yogyakarta reported that adding *Moringa oleifera* powder to baby food made a positive increase of body mass index to an average value around of 13-14 children from 30 respondents ([Rahayu & Nurindahsari 2018](#)). The study conducted at the Piyungan Community Health Centre showed a similar result. Mothers with higher educational status tend to choose complementary food that rich in *Moringa oleifera* powder for their babies which can increase toddler height by 0.476 cm to 0.594 cm ([Muliawati & Sulistyawati 2019](#)). *Moringa oleifera* contains minerals (such as calcium, iron, and sodium), vitamins C and E, beta carotene, as well as antioxidants (flavonoid acids, phenolic acids, glucosinolates, isothiocyanates, and saponins) ([Leone et al. 2015](#)). Various compounds in *Moringa oleifera* leaves powder can affect genomic processes (transcriptomic, proteomic, and metabolomic) as well as inflammatory processes that occur specifically in stunting ([Susanto et al. 2017](#)). Fulfilment of nutrients for infants needs to be done so that it does not cause inflammation and disruption of genomic processes that occur in stunting.

The utilization of *Moringa oleifera* leaves powder for stunting is currently being carried out, but there is no further study summarize the nutrigenomics and molecular biology aspects. Therefore in this literature review, we will discuss the nutrigenomic and molecular biology aspects of *Moringa oleifera* leaves powder as supplementation for stunted children. The review is written because no literature thoroughly discusses the ingredients contained in *Moringa oleifera* leaves against the pathophysiology of stunting.

MATERIALS AND METHODS

The writing method used was a literature review with relevant articles from search engines such as pubmed.com, sciencedirect.com, and scholar.google.com. We searched for the keywords "stunting", "nutrigenomics", "biomolecular", and "*Moringa oleifera*". Based on the search results, we filtered the literature and only use articles in proceedings or journals both in English and Bahasa Indonesia. Then sorting was done by understanding the abstract and article contents. Inclusion criteria were all research articles concerning the relationship of nutrition to *Moringa oleifera* with stunting. Articles exceeding the last 10 years were eliminated unless there was no new research that contradicts the contents of the article. Of the 71 articles reviewed, 60 articles were found to be suitable as references.

RESULTS AND DISCUSSION

Stunting

Stunting is a state of malnutrition so that individuals will be short below the

average growth chart. This condition is one of the contributors that cause an increase in early childhood death due to malnutrition which continues into the terminal phase ([Susanto et al. 2017](#)).

The level of parental education influences preferences in offering food for children's nutrition. Most parents only provide exclusive breastfeeding for up to six months, which makes breast milk not enough to support the nutrition of children. On the other hand, lack of socio-economic conditions makes parents unable to provide decent food for their children, so that children tend to be malnourished. Complementary foods are very important to be given to babies under one year old because complementary foods will support the maturation of myelination of brain development, thereby reducing cognitive deficits in child development ([Soetjningsih 1995](#)).

Complementary foods should be given to infants, especially those 6-24 months old, to meet the nutritional needs of the child ([Mufida et al. 2015](#)). Most parents do not understand how to arrange nutritional needs according to the child's age so that children's nutrition is prone to developing failure ([Maki A 2014](#)). This is a reason to provide children's nutrition during the growth period because it will be an investment in the future condition of children ([Shekar et al. 2017](#)). In the process of child development, sufficient micronutrient content in complementary foods is needed so that fortification is necessary ([Kim et al. 2009](#)). Micronutrients and proteins play important role in the body, so if a child is suffering micronutrient deficiency, it triggers decreasing amino acid regulation in the body ([Reddy et al. 2018](#)). In addition, protein functions as a stabilizer and buffer in the body, so it has a role as a guard in the immune system such as antibodies ([Laurus et al. 2016](#)).

If the nutrient requirement containing protein and micronutrients is not fulfilled, the child will be susceptible to stunting. Stunting tends to increase susceptibility to infection due to the release of proinflammatory cytokines in the form of IL-1, IL-6, and IL-8 which cause children to have the potential to develop metabolic syndrome in the future ([Abd El-Maksoud et al. 2017](#)). This incident requires the ability of parenting care to provide proper nutrition to children so that children do not become malnourished ([Glover-Amengor et al. 2017](#)).

***Moringa oleifera* Leaves**

Moringa oleifera is a cultural-magical-medical plant that has many bioactive substances and can live in a variety of soil conditions ([Daba 2016](#)). According to research in Uganda, the *Moringa oleifera* plant can be used to cure 24 chronic metabolic diseases and one of them is stunting ([Kasolo et al. 2010](#)). The nutrient of *Moringa oleifera* is fairly complete, namely protein, micronutrients, natural minerals, and antioxidants ([Leone et al. 2015](#)). This is supported by research in Tanzania, the nutritional content of *Moringa oleifera* is higher than oranges, eggplants, spinach, cabbage, and peanuts ([Shija et al. 2019](#)). The nutritional value per 100 g of *Moringa oleifera* leaves extract consists of carbohydrate 9.1 g, dietary fiber 2.1 g, fat 1.7 g, and protein 8.1 g. The vitamin content of *Moringa oleifera* are vitamin A 80 µg, thiamine 0,103 mg, riboflavin 0,112 mg, niacin 1.5 pantothenic acids 0.48 mg, vitamin B6 0.129 mg, folate 41 µg, and vitamin C 8,6 mg ([Abbas et al. 2018](#)). *Moringa oleifera* is relatively easy to be made into powder and efficient because it only dried with the sun and then blended with the machine, the nutritional content is similar when compared to conventional methods (method with additional 35-55°C heating in a machine) ([Susanto et al. 2017](#)). Thus, this plant is practically used in households, contains enough polyphenols for infant nutrition, and can meet iron needs for anemia ([Teshome et al. 2009](#); [Zongo et al. 2013](#); [Rahayu & Nurindahsari 2018](#)). Five grams of *Moringa oleifera* powder as complementary food at a two-phase meal every day already

fulfil 75% of the nutritional needs of babies after breastfeeding (Amagloh et al. 2012). The use of *Moringa oleifera* leaves powder for overcoming stunting for 4 months is considered feasible (Rosha et al. 2016). Side effects such as diarrhoea rarely complained because *Moringa oleifera* leaves powder also act as antidiarrheal (Joung et al. 2017).

Moringa oleifera leaves have the potential benefit to modify epigenetics. They also have benefits as active substances in the nutrigenomic approach, besides its anti-inflammatory, antioxidant, and antianemic effect.

Stunting can be triggered by the presence of contaminants in food because there are pathogenic microbes. The contaminated food will enter the digestive tract which triggers an imbalance in the composition of the intestinal microbiota to change structure, function, and ability to gut epithelial regeneration that changes metagenomic and metatranscriptomic processes. There are two pathways from these metagenomic and metatranscriptomic changes. The first pathway explains the disruption of tight junctions and enterocytes that increase intestinal permeability and then increase microbial translocation. The increased translocation of microbe increase lipopolysaccharide (LPS), Endocab, sCD14 receptor for LPS, sCD163 receptor for LPS, and trigger gut mucosa inflammation. The inflammation of mucosa can increase neopterin, ATT (specific protein), myeloperoxidase (MPO), and can trigger systemic cascade and subsequent increased level of C-reactive proteins (CRP) and alfa 1-acid glycoprotein (AGP). This process increases the child's nutritional needs and creates growth hormone resistance, increases hepcidin, and decreases EPO (erythropoiesis). The second pathway explains the occurrence of metagenomic and metatranscriptomic changes and causes intestinal villi

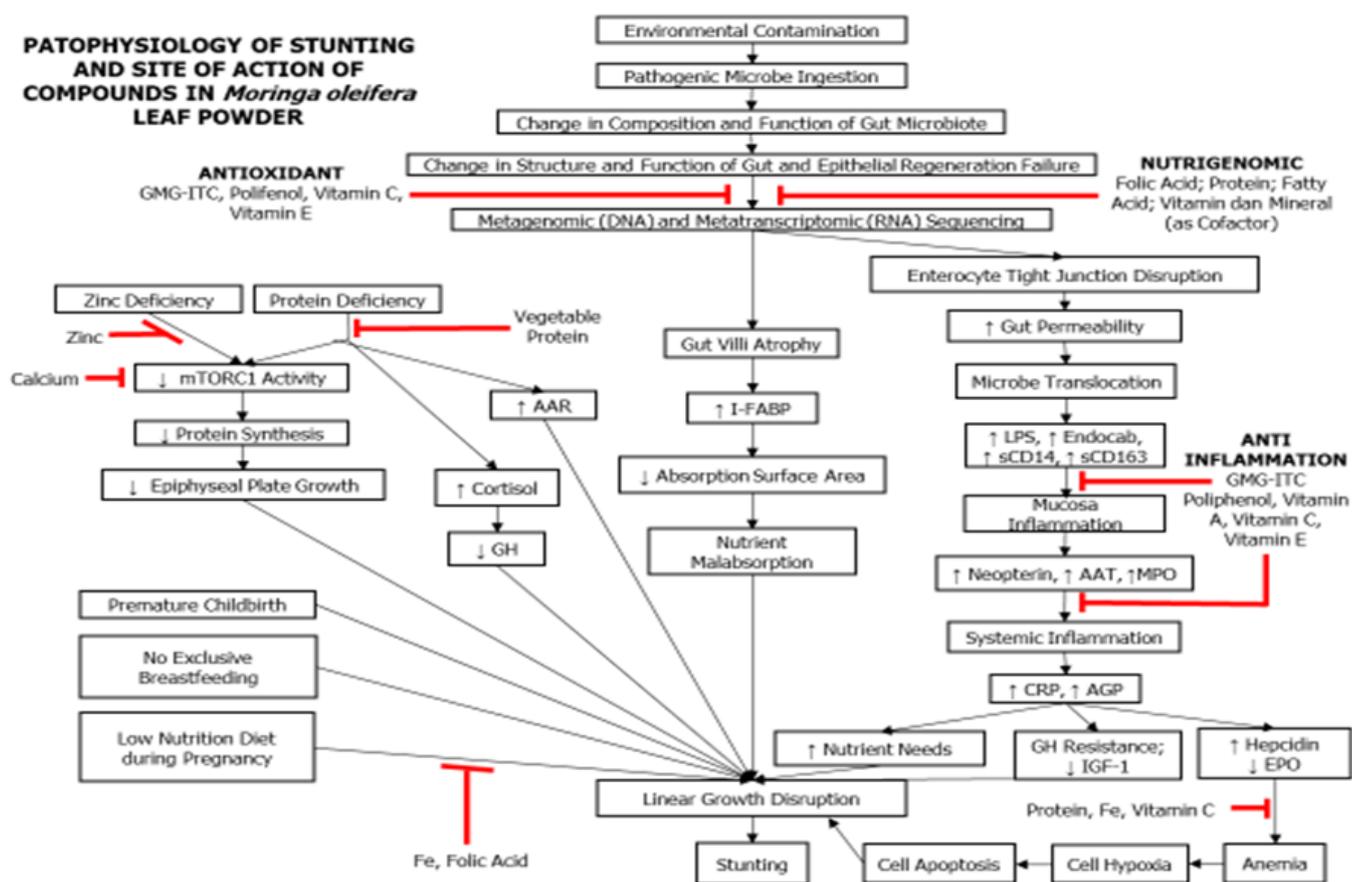


Figure 1. Mechanism Action Review of *Moringa oleifera* leaves powder in Stunting Pathophysiology at Molecular, Cellular, and Physiological Level via Nutrigenomic, Antioxidant, Antiinflammation, and Antianemia Mechanism (Sedgh et al. 2000; Mohan 2013; Ma et al. 2020; Prendergast et al. 2015; Gonzalez et al. 2015; Saini et al. 2016; Denardo et al. 2015).

atrophy can increase intestinal fatty-acid binding protein (iFABP) and decreases the absorption surface area which causes malabsorption of nutrients consumed by children. Increased hepcidin and decreased EPO will cause anemia which triggers cell hypoxia and cell apoptosis causes malabsorption of the nutrients consumed. As a result, there is an increase in nutrition due to cell apoptosis, which if not fulfilled the nutritional adequacy disrupts the linear growth of the child so that it becomes stunting. In addition, stunting can be caused by zinc deficiency and protein deficiency as well as premature births that do not receive exclusive breastfeeding and lack nutrition during pregnancy. *Moringa oleifera* has antioxidant and nutrigenomic mechanisms that inhibit the metagenomic and metatranscriptomic sequences. In addition, the anti-inflammatory effect of *Moringa oleifera* inhibits mucosal and systemic inflammation. Another content in the form of calcium inhibits the decrease in mTOR complex 1 (mTORC1) activity which increases protein synthesis and increases the growth of the epiphyseal plate which results in increased linear growth of children. This explanation is described in Figure 1. ([Sedgh et al. 2000](#); [Mohan 2013](#); [Ma et al. 2020](#); [Prendergast et al. 2015](#); [Gonzalez et al. 2015](#); [Saini et al. 2016](#); [Denardo et al. 2015](#); [Stefano et al. 2019](#)).

Mechanism in Nutrigenomic Aspect

The pathogenesis of stunting involves the changes in deoxyribonucleic acid (DNA). The genome can be modified through nutrigenomics where the nutrients affect the genome stability. Nutrigenomics is closely related to epigenetics. Nutrigenomics is the study of the effects of substances contained in food on gene expression. Whereas epigenetics refers to variations derived from DNA that regulate chromosome architecture and modify gene expression without changing the underlying DNA sequence. Epigenetics can be distinguished from genetic mutations. Epigenetics does not produce a change in the nucleotide sequence because they consist of modifications such as DNA methylation, histone deacetylation, gene silencing by microRNA (miRNA), and maintaining chromosome stability ([Gonzalez et al. 2015](#); [Saini et al. 2016](#)). DNA wrapped around a protein called a histone. Modification of histones refers to how closely the DNA strands are wrapped around the histones. Modified histones are known to affect protein transcription, DNA repair processes, DNA replication, and chromatin condensation. Dietary factors directly influence these epigenetic mechanisms ([Saini et al. 2016](#)). Nutrition can change gene expression in several ways, such as: acting as a ligand for transcription factor receptors; being metabolized in the primary or secondary metabolic pathways thereby changing the concentration of substrates or intermediates; and changing the signal transduction pathway. There are three important influences that can change the way genes are expressed, namely what genes are turned on, how the messages in genes are transcribed, and what post-translocation effects in cells by the expression of these genes ([Gonzalez et al. 2015](#)).

In nutrigenomics aspects, the folate contained in *Moringa oleifera* leaves powder plays a role in epigenetic modification such as DNA methylation, through the pathway as described in Figure 2 and Figure 3. Figure 2 described approximately 50% of S-adenosylmethionine (SAM) is metabolized in the liver. SAM is metabolized to S-adenosylhomocysteine (SAH) which is then metabolized to homocysteine. Homocysteine can either be metabolized to cystathionine and then cysteine or methionine. *Moringa oleifera* leaves powder also contains vegetable protein which acts as a ligand in the DNA sequence promoter which then starts DNA transcription for protein production again ([Huang et al. 2014](#)). This reproduced protein plays a role in overcoming stunting ([Ma et al. 2020](#)). In addition to protein, the fatty acids in

Moringa oleifera leaves powder also have a similar ability to affect DNA transcription (Mohan 2013). The fatty acids contained in *Moringa oleifera* leaves powder is ω -3 Poly Unsaturated Fatty Acid (PUFA) which is of α -linolenic as shown in Figure 4. Long chain ω -3 fatty acids such as eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) are synthesized de novo in organisms from α -linolenic fatty acids (Rodríguez-Cruz & Serna 2017). The vitamins and minerals contained in *Moringa oleifera* leaves powder also play a role in nutrigenomics because one of its functions is to increase enzyme efficiency. Vitamins are cofactors for enzymes, enzymes classified as protein, and proteins can be changed due to genetic changes and these genetic changes affect protein function. The formation of an active cofactor requires an active enzyme, moreover for the enzyme to function at its maximum capacity, an adequate active cofactor must necessarily exist (Gonzalez et al. 2015).

Folic Acid has a role in the nutrigenomic process. This folic acid enters the nucleus which triggers dihydrofolic acid (DHF) to be converted into tetrahydrofuran (THF). Later, THF with the help of vitamin B6 and vitamin B2 will be converted to 5,10-methylene THF and combine with betaine and homocysteine to become B12. Vitamin B12 and B6 will be converted into methionine which then is converted into S-adenosylmethionine (SAM) and by the DNA methyltransferase (DNMTase) and SAM enzymes enter the cell nucleus and undergo epigenetic modification which plays a role in the nutrigenomic process (Huang et al. 2014). This explanation is described in Figure 2.

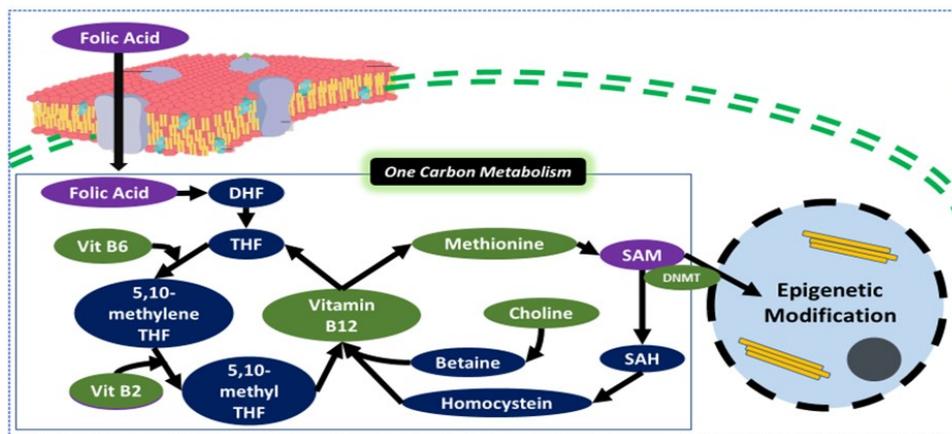


Figure 2. S-adenosylmethionine (SAM) Produced in One Carbon Metabolism of Folic Acid, Act in Cell Nucleus to Induce Epigenetic Modification (Modified From: Huang et al. 2014).

S-adenosylmethionine (SAM) that enters the nucleus causes genomic methylation and metabolic methylation. The genomic methylation cause chromatin remodeling and histone modifications. Histone modification trigger activated gene silencing stunting. An increase in mTOR complex 1 (mTORC1) in the presence of glucose, growth factor, and amino acids also increase mTORC1 activity which activates Unc -51 Like Autophagy Activating Kinase 1 (ULK1) and causes a decrease in autophagy so that cells do not eat themselves and then trigger 4E-Binding Protein (4EBP) to synthesize protein and contribute to child development (Huang et al. 2014). This explanation is described in Figure 3.

The fatty acids contained in *Moringa oleifera* leaf powder is ω -3 Polyunsaturated Fatty Acid (PUFA) which is α -linolenic as shown in Figure 4. Long chain ω -3 fatty acids such as eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) are synthesized de novo in organisms from α -

linolenic fatty acids (Rodríguez-Cruz and Serna, 2017). EPA and DHA trigger peroxisome proliferator-activated receptor gamma (PPAR- γ) activity which then enter the nucleus to induce adiponectin production. EPA and DHA also increase beta-oxidation and reduce lipid accumulation through adenosine monophosphate protein kinase (AMPK) activity. Inhibition of prostaglandins E2 (PGE2) formation also occurs through arachidonic acid (AA) decrease. EPA and DHA also inhibit lipopolysaccharide (LPS) and increase the activity of G-proteins couples receptors 120 (GPR120) so that it inhibits nuclear factor kappa beta (NFkB) and do not form interleukin-6 (IL-6) and monocyte chemoattractant protein 1 (MCP1). The vitamins and minerals contained in *Moringa oleifera* leaf powder also play a role in nutrigenomics because one of its functions is to increase enzyme efficiency. Vitamins are cofactors for enzymes, enzymes classified as protein, and proteins can be changed due to genetic changes and affect protein function. The formation of an active cofactor requires an active enzyme, moreover for the enzyme to function at its maximum capacity, an adequate active cofactor must necessarily exist (Gonzalez et al. 2015).

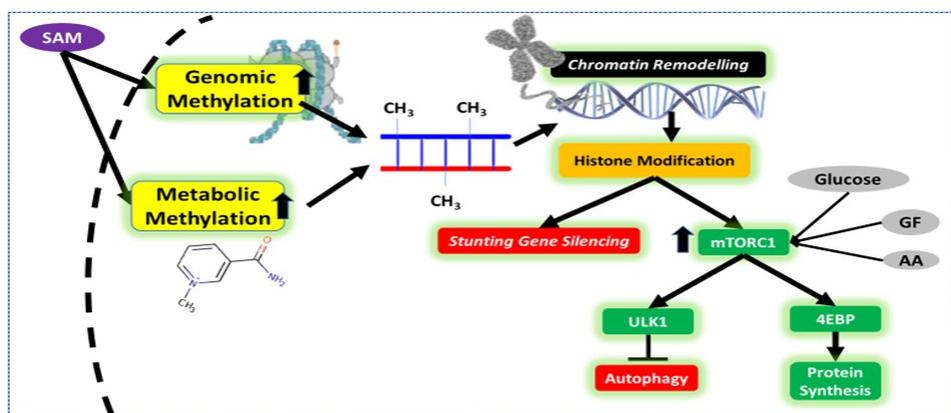


Figure 3. Mechanism of Action of SAM in Nutrigenomics (Modified From: Huang et al. 2014).

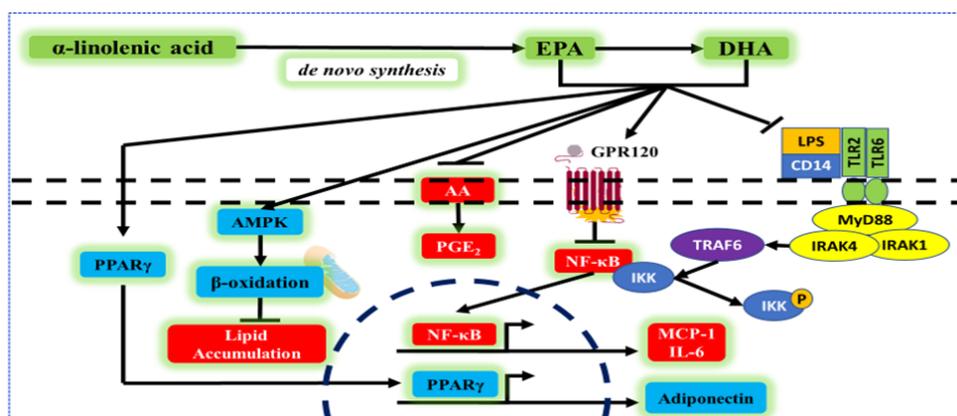


Figure 4. Mechanism of Action of α -linolenic acid in Nutrigenomics (Modified From: Rodríguez-Cruz & Serna 2017).

Mechanism in Biochemical Aspect

Antioxidants are compounds that inhibit oxidation and thus prevent oxidative stress which causes DNA damage (Wang et al. 2017). The antioxidant agents contained in *Moringa oleifera* leaves powder are polyphenols, vitamin C, vitamin E, and glucomoringin-isothiocyanate (GMG-ITC). Polyphenols induce antioxidant effects through the mechanism of hydrogen atom transfer (HAT), single electron transfer (SET), and transition metal chelation (TMC) (Leopoldini et al. 2011). Polyphenols are useful in

reducing lipid peroxide and increasing the concentration of glutathione (GSH), along with decreasing the activity of SOD and catalase enzymes. In addition, polyphenols can also reduce the concentration of serum malondialdehyde (MDA) (Ma et al. 2020). *Moringa oleifera* leaf powder rich in polyphenol (such as flavonoids quercetin, isorhamnetin, and kaempferol glycosides) and phenolic acids (Sedgh et al. 2000; Ma et al. 2020). Vitamin C and E work together as antioxidants. Vitamin E converts lipid free radicals such as peroxy (LOO•) and alkoxy (LO•) into lipid hydroperoxide (LOOH) and lipid hydroxide (LOH) through the transfer of hydrogen atoms to its structure. Vitamin E which has lost its hydrogen atom will be renewed again by vitamin C so that vitamin E contains the hydrogen atom again and is ready to convert free radicals again (Valko et al. 2004).

GMG-ITC is one of the dominant types of glucosinolate found in *Moringa oleifera* leaves powder. GMG that is converted to ITC has active antioxidant effects on the body (Figure 5). ITC causes an increase in expression of erythroid 2-related factor 2 (Nrf2) which then translocates to the nucleus and releases its bond with KEAP1 in the cytoplasm. Inside the nucleus, Nrf2 binds to small Maf proteins (sMaF) and undergo phosphorylation which triggers the transcription of several compounds that are essential in the process of lowering oxidative stress. Compounds that will be enhanced are superoxide dismutase-1 (SOD-1), GSH/GSR, NAD(P)H:quinone oxidoreductase 1 (NQO1), glutaredoxin (GLRX), heme oxygenase-1 (HO-1), thioredoxin reductase/thioredoxin (TXNRD/TXN), and nicotinamide adenine dinucleotide phosphate (NADPH) (Saini et al. 2016).

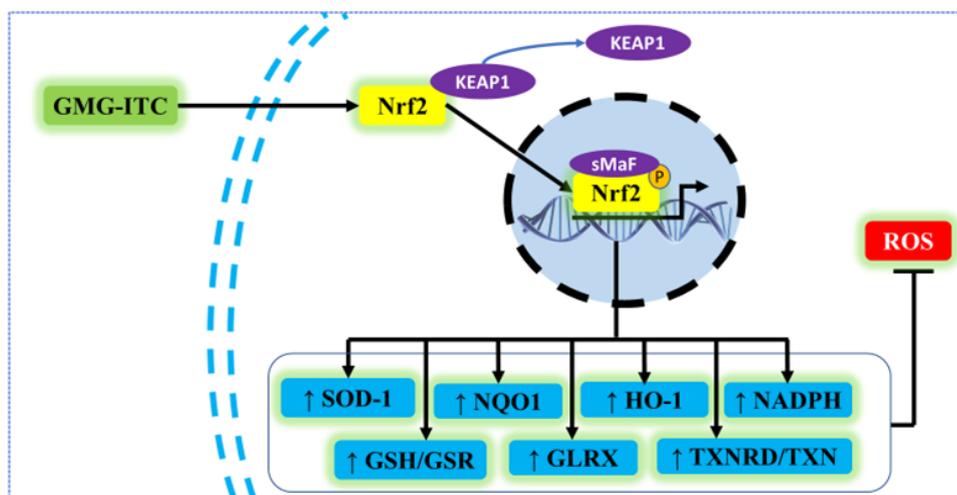


Figure 5. Mechanism of Action of GMG-ITC as an Antioxidant (Modified From: Saini et al. 2016).

Inflammation also plays an important role in the pathophysiology of stunting, by inducing Growth Hormone (GH) resistance, an increase in the body's nutritional need, and also anemia, and all of these results in cell apoptosis as shown in Figure 1. Inflammation begins with the binding of lipopolysaccharides (LPS) to TLR4. The anti-inflammatory agents in *Moringa oleifera* leaf powder which plays a role in inhibiting stunting are vitamin E, vitamin C, GMG-ITC, and All-E lutein as described in Figure 6 (Prendergast et al. 2015). Vitamin E and C play a role in inhibiting NF- κ B, where vitamin C acts directly inside the nucleus and vitamin E through PKC- θ inhibition. Meanwhile, GMG-ITC and All-E lutein reduce TLR4 expression which will cause a decrease in NF- κ B activation through MAPK (ERK/JNK) and I κ B α . The suppression of NF- κ B will inhibit the expression of messenger RNA (mRNA) and results in decreased inducible nitric oxide synthase (iNOS),

cyclooxygenase-2 (COX-2), and thereby decrease the release of TNF α , IL-1 β , IL-6, and IL-8 (Mohan 2013). GMG-ITC will also enhance IKK activation which will reduce the phosphorylation of I κ B and will repeat the process of NF- κ B inhibition again. This explanation is described in Figure 6. (Mohan 2013).

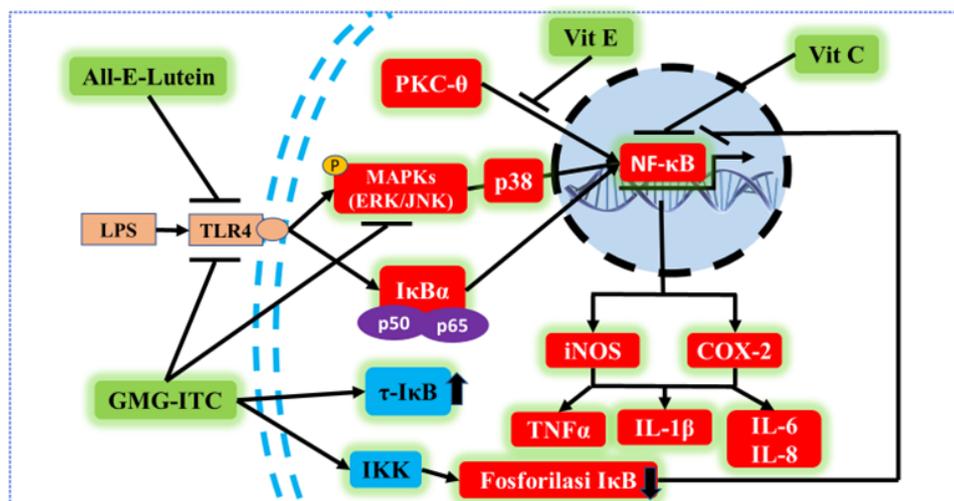


Figure 6. Mechanism of Action of GMG-ITC, All-E-Lutein, Vitamin C, and Vitamin E as An Antiinflammation

Moringa oleifera may acts as an anti-anemia through direct and indirect mechanisms. The indirect mechanism occurs through the depletion of IL-6 synthesis which is induced by GMG-ITC, thereby inhibits hepcidin expression in hepatocytes (Ganz & Nemeth 2011). The direct anti-anemia mechanism involves several active compounds in *Moringa oleifera* leaves powder, such as vegetable protein, iron, and vitamin C (Idohou-Dossou et al. 2011; Saini et al. 2014). Vegetable protein will be converted to amino acid (AA) in the digestive tract which then contributes to erythropoiesis through the synthesis of transferrin, protoporphyrin, and globin (Idohou-Dossou et al. 2011). Iron, in addition to its role in erythropoiesis (the formation process of erythrocytes with iron that binds oxygen), may also suppress the synthesis of hepcidin mRNA in hepatocytes. Reduced hepcidin level raises the ferroprotein (FPN) activity. It facilitates iron to enter enterocytes into the blood plasma and trigger erythropoiesis in the bone marrow. This effect incites the potential of the iron contained in *Moringa oleifera* leaves powder to be better than the iron contained in ferric citrate (a potent drug for anemia at the moment) (Saini et al. 2014). Vitamin C acts as a nonheme iron enhancer. Iron in *Moringa oleifera* leaves powder is classified as nonheme iron (Fe³⁺) because it comes from a plant. In order to enter the enterocytes, this type of iron needs to be converted into the form of Fe²⁺. The conversion of Fe³⁺ to Fe²⁺ occurs with the help of duodenal cytochrome b (DCYTB), a ferric reductase enzyme. This enzyme requires vitamin C as a cofactor by donating its electrons and reduce Fe³⁺ to Fe²⁺, therefore Fe²⁺ may be transported by divalent metal transporter-1 (DMT-1). The vitamin C compound is already contained in *Moringa oleifera* leaves powder to facilitate the conversion of the iron and help its absorption inside the gut (Idohou-Dossou et al. 2011).

The Advantages of *Moringa oleifera* Leaves Powder

The development of innovative use of *Moringa oleifera* leaves powder as an additional ingredient for complementary food has the potential to fulfil the baby's nutritional needs and prevent stunting. The use of *Moringa oleifera* leaves powder as an alternative to supplement food for stunting children may

ease the country's burden in the massive import of green beans and milk which is also difficult to reach by the middle to lower economic class ([Nasmiati et al. 2014](#)).

According to the survey results of food consumption in Central Java Province, the majority of people consume foods containing vegetable protein compared to animal protein meat that relatively more expensive ([Rosha et al. 2016](#)). The vegetable protein that is often consumed is in the form of processed soybeans. According to a previous study by Swarinastiti et al. ([2018](#)), tempeh consumption alone causes a 4.49-times risk of stunting in children, because tempeh is low in amino acids (methionine and cysteine) and if the protein synthesis is not optimal, the susceptibility of growth faltering will be higher ([Swarinastiti et al. 2018](#)). Based on the latest research, the dietary formulation to improve stunting condition is still by a combination of staple foods (corn, rice porridges, and/or yams) with vegetable protein sources (tofu and tempeh), and add *Moringa oleifera* leaves powder to complete all of the nutritional needs with the ratio of 60:30:10 to meet the minimum calories requirement by WHO that is 200-300 kcal ([Stefano et al. 2019](#); [Netshiheni et al. 2019](#)).

The recommended food processing for children is steaming because it is easily pulverized and no protein denaturation compared to the deep frying method which may lower the micronutrient contents by 5-40% ([Mohan 2013](#)). Vegetable protein can be given starting from 6 months old, meanwhile animal protein can be safely given at the age of eight months old because it contains gluten that is difficult to digest. In addition, meat that is available in the market may contain preservatives such as monosodium glutamate (MSG) ([Ganasen et al. 2018](#)). MSG may trigger a slowdown in linear growth that causes suboptimal growth in children ([Chakraborty 2019](#)). Preserved meat may also induce metabolic syndrome in the future, which is also a complication of stunting ([Chibisov et al. 2019](#)). *Moringa oleifera* leaves powder contains zinc and iron, thereby is the potential to be the main source of complementary food ([Mawouma et al. 2017](#)).

The Limitations of *Moringa oleifera* Leaves Powder

In the process of giving *Moringa oleifera* leaves powder as a complementary food, the limitation that arises is the bitter taste. On the other hand, the bitter taste is a form of taste recognition in children. This process also supports the development of children's taste sensation. To overcome this limitation, the consumption of *Moringa oleifera* leaves powder can be done by adding the powder in several food segments and also estimates the children's eating habits and times ([Probowati et al. 2016](#)).

Complementary food consumption can be adjusted by arranging a daily schedule, such as a combination of fruit juice with honey and additional *Moringa oleifera* leaves powder in the morning, and a combination of porridge with milk or coconut milk and additional *Moringa oleifera* leaves powder in the afternoon or evening. This consumption should be done before breastfeeding in order to avoid the feeling of fullness from the baby and eventually refuse to eat ([Oyeyinka & Oyeyinka 2018](#)). The principle of giving complementary food fortification of *Moringa oleifera* leaves powder is to provide a good experience for the children and minimize the bad experience ([Loya & Nuryanto 2017](#)). The effects of this *Moringa oleifera* leaves powder will be optimal if the consumption takes place constantly every day for four months ([Joung et al. 2017](#)).

This literature review has discussed some pathways that are considered to treat stunting, such as nutrigenomics, anti-inflammatory, antioxidants, and antianemia. However, cytokines and molecules included in this literature

review have not been widely discussed, so it is necessary to conduct further literature studies.

CONCLUSION

Moringa oleifera leaves powder is very beneficial in preventing stunting. The consumption of *Moringa oleifera* leaves powder as a fortification in complementary food has the potential through nutrigenomic and biology molecular aspects with its mechanisms as an antiinflammation, antioxidant, and antianemia agent. Therefore, further research related to these aspects must be developed in the future.

AUTHORS CONTRIBUTION

Data gathering and idea owner of this study was conducted by Agus Indra Yudhistira Diva Putra, Nyoman Budhi Wirananda Setiawan, Made Indira Dianti Sanjiwani, Agung Wiwiek Indrayani. Writing and submitting manuscript was carried out by Agus Indra Yudhistira Diva Putra, Nyoman Budhi Wirananda Setiawan, Made Indira Dianti Sanjiwani, Agung Wiwiek Indrayani. In addition, editing and final draft approval was conducted by Agung Wiwiek Indrayani and Ida Ayu Ika Wahyuniari.

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CONFLICT OF INTEREST

There is no competing interest regarding manuscript.

REFERENCES

- Abbas, R.K., Elsharbasy, F.S., & Fadlelmula, A.A. 2018. Nutritional values of moringa oleifera, total protein, amino acid, vitamins, minerals, carbohydrates, total fats and crude fiber, under the semi-arid conditions of Sudan. *Journal of Microbial & Biochemical Technology*, 10 (2), pp. 56-58.
- Abd El-Maksoud, A. M., Khairy, S. A., Sharada, H. M., Abdalla, M. S. & Ahmed, N. F. 2017. Evaluation of pro-inflammatory cytokines in nutritionally stunted Egyptian children. *Egyptian Pediatric Association Gazette*, 65, pp. 80-84.
- Amagloh, F. K., Hardacre, A., Mutukumira, A. N., Weber, J. L., Brough, L. & Coad, J. 2012. A household-level sweet potato-based infant food to complement vitamin A supplementation initiatives. *Maternal & child nutrition*, 8, pp. 512-521.
- Chakraborty, S. P. 2019. Patho-physiological and toxicological aspects of monosodium glutamate. *Toxicology Mechanisms and Methods*, 29, pp. 389-396.
- Chibisov, S., Singh, M., Singh, R. B., Halabi, G., Horiuchi, R. & Takahashi, T. 2019. Functional food security for prevention of obesity and metabolic syndrome. *The Role of Functional Food Security in Global Health*. Elsevier.
- Daba, M. 2016. Miracle tree: A review on multi-purposes of *Moringa oleifera* and its implication for climate change mitigation. *J. Earth Sci. Clim. Change*, 7.
- De Onis, M. & Branca, F. 2016. Childhood stunting: a global perspective. *Maternal & child nutrition*, 12, pp. 12-26.
- Denardo, A., Arosio, P. & Carmona, D. F. 2015. Production of recombinant human BMP6 and peptides for the study of heparin binding activity. Thesis, Universita Degli Studi Di Bresica, Italy.

- Dhakar, R. C., Maurya, S. D., Pooniya, B. K., Bairwa, N. & Gupta, M. 2011. Moringa: The herbal gold to combat malnutrition. *Chronicles of Young Scientists*, 2.
- Ganasen, M., Togashi, H., Takeda, H., Asakura, H., Tosha, T., Yamashita, K., Hirata, K., Nariai, Y., Urano, T. & Yuan, X. 2018. Structural basis for promotion of duodenal iron absorption by enteric ferric reductase with ascorbate. *Communications biology*, 1, pp. 1-12.
- Ganz, T. & Nemeth, E. 2011. The hepcidin-ferroportin system as a therapeutic target in anemias and iron overload disorders. *Hematology 2010, the American Society of Hematology Education Program Book*, 2011, pp. 538-542.
- Glover-Amengor, M., Aryeetey, R., Afari, E. & Nyarko, A. 2017. Micronutrient composition and acceptability of Moringa oleifera leaf-fortified dishes by children in Ada-East district, Ghana. *Food Science & Nutrition*, 5, pp. 317-323.
- Gonzalez, M. J., Miranda-Massari, J. R., Duconge, J., Rodriguez, J. R., Cintron, K., Berdiel, M. J. & Rodriguez, J. W. 2015. Nutrigenomics, Metabolic Correction and Disease. *Journal of Restorative Medicine*, 4, pp. 74-82.
- Huang, W.-L., Tung, C.-W., Liaw, C., Huang, H.-L. & Ho, S.-Y. 2014. Rule-based knowledge acquisition method for promoter prediction in human and drosophila species. *The Scientific World Journal*, 2014, 327306.
- Idohou-Dossou, N., Diouf, A., Gueye, A., Guiro, A. & Wade, S. 2011. Impact of daily consumption of Moringa (Moringa oleifera) dry leaf powder on iron status of Senegalese lactating women. *African journal of food, agriculture, nutrition and development*, 11, pp. 4985-4999.
- Joung, H., Kim, B., Park, H., Lee, K., Kim, H.-H., Sim, H.-C., Do, H.-J., Hyun, C.-K. & Do, M.-S. 2017. Fermented Moringa oleifera decreases hepatic adiposity and ameliorates glucose intolerance in high-fat diet-induced obese mice. *Journal of medicinal food*, 20, pp. 439-447.
- Kasolo, J. N., Bimenya, G. S., Ojok, L., Ochieng, J. & Ogwal-Okeng, J. W. 2010. Phytochemicals and uses of Moringa oleifera leaves in Ugandan rural communities. *Journal of Medicinal Plants Research*, 4, pp. 753-757.
- Kemenkes, R. 2013. Laporan riset kesehatan dasar tahun 2013 [2013 Basic Health Research report]. *Jakarta: Balai Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI*.
- Kemenkes, R. 2018. Situasi balita pendek (Stunting) di Indonesia [The situation of stunting in Indonesia]. *Buletin Jendela Data dan Informasi Kesehatan. Semester I*.
- Kim, M. S., Wu, K. Y., Auyeung, V., Chen, Q., Gruppuso, P. A. & Phornphutkul, C. 2009. Leucine restriction inhibits chondrocyte proliferation and differentiation through mechanisms both dependent and independent of mTOR signaling. *American Journal of Physiology-Endocrinology and Metabolism*, 296, pp. E1374-E1382.
- Kou, X., Li, B., Olayanju, J. B., Drake, J. M. & Chen, N. 2018. Nutraceutical or pharmacological potential of Moringa oleifera Lam. *Nutrients*, 10, pp. 343.
- Kuswanto, W. R. a. K. R. & Widanti, Y. A. 2018. Penambahan puree daun kelor (moringa oleifera) dan puree pisang ambon untuk formula MPASI (Makanan Pendamping ASI) [Addition of Moringa leaf puree (moringa oleifera) and Ambon banana puree to formula complementary foods (ASI)]. *JITIPARI (Jurnal Ilmiah Teknologi dan Industri Pangan UNISRI)*, 3.
- Laurus, G., Fatimah, S. N. & Gurnida, D. A. 2016. Pattern of Energy and Protein Intake among Stunted Children Aged 3–5 Years in Jatinangor. *Althea Medical Journal*, 3, pp. 364-370.

- Leone, A., Spada, A., Battezzati, A., Schiraldi, A., Aristil, J. & Bertoli, S. 2015. Cultivation, genetic, ethnopharmacology, phytochemistry and pharmacology of *Moringa oleifera* leaves: An overview. *International journal of molecular sciences*, 16, pp. 12791-12835.
- Leopoldini, M., Russo, N. & Toscano, M. 2011. The molecular basis of working mechanism of natural polyphenolic antioxidants. *Food Chemistry*, 125, pp. 288-306.
- Loya, R. R. P. & Nuryanto, N. 2017. *Pola Asuh Pemberian Makan pada Balita Stunting Usia 6–12 bulan di Kabupaten Sumba Tengah Nusa Tenggara Timur*. Diponegoro University.
- Ma, Z., Ahmad, J., Zhang, H., Khan, I. & Muhammad, S. 2020. Evaluation of phytochemical and medicinal properties of *Moringa* (*Moringa oleifera*) as a potential functional food. *South African Journal of Botany*, 129, pp. 40-46.
- Maki A, M. 2014. Hubungan antara pendapatan orang tua dengan status gizi pada siswa SDN II Tenggong Rejotangan Tulungagung [The relationship between parents' income and nutritional status of SDN II Tenggong Rejotangan Tulungagung students]. *Jurnal Pendidikan Olabraga dan Kesehatan*, 2.
- Mawouma, S., Ponka, R. & Mbofung, C. M. 2017. Acceptability and solubility of iron and zinc contents of modified *Moringa oleifera* sauces consumed in the Far-north region of Cameroon. *Food science & nutrition*, 5, pp. 344-348.
- Mitra, M. 2015. Stunting problems and interventions to prevent stunting (a Literature Review). *Jurnal Kesehatan Komunitas*, 2, pp. 254-261.
- Mohan, N. 2013. Dietary Nutrients: More Than Just nourishment. NISCAIR -CSIR, 50, pp. 34-35.
- Mufida, L., Widyaningsih, T. D. & Maligan, J. M. 2015. Prinsip Dasar Makanan Pendamping Air Susu Ibu (MP-ASI) Untuk Bayi 6–24 Bulan: Kajian Pustaka [Basic Principles of Complementary Breastfeeding (MP-ASI) for Infants 6–24 Months: Literature Review]. *Jurnal Pangan dan Agroindustri*, 3.
- Muliawati, D. & Sulistyawati, N. 2019. The use of *Moringa oleifera* extract to prevent stunting in toddler *Jurnal Kesehatan Madani Medika*, 10, pp. 123-131.
- Nasmiasi, C., Ginting, R. & Rahman, A. 2014. Analisis Produksi Dan Ketersediaan Serta Kebutuhan Kedelai Dalam Kaitannya Dengan Ketahanan Pangan Di Provinsi Sumatera Utara [Analysis of Soybean Production and Availability and Needs in Relation to Food Security in North Sumatra Province]. *JURNAL AGRICA*, 7, pp. 13-25.
- Netshiheni, K. R., Mashau, M. E. & Jideani, A. I. O. 2019. Nutritional and sensory properties of instant maize porridge fortified with *Moringa oleifera* leaves and termite (*Macrotermes falciger*) powders. *Nutrition & Food Science*.
- Oyeyinka, A. T. & Oyeyinka, S. A. 2018. *Moringa oleifera* as a food fortificant: Recent trends and prospects. *Journal of the Saudi Society of Agricultural Sciences*, 17, pp. 127-136.
- Prendergast, A. J., Humphrey, J. H., Mutasa, K., Majo, F. D., Rukobo, S., Govha, M., Mbuya, M. N., Moulton, L. H. & Stoltzfus, R. J. 2015. Assessment of environmental enteric dysfunction in the SHINE trial: methods and challenges. *Clinical Infectious Diseases*, 61, pp. S726-S732.
- Probowati, R., Wibowo, H., Ningtyas, S. F., Ratnawati, M. & Nursalam, N. 2016. Role Attainment Ibu dalam Pemberian MP-Asi dengan Peningkatan Berat Badan Bayi Usia 6-12 Bulan [Mother's Role Attainment in Giving MP-Asi with Increasing Body Weight for Infants aged 6-12 Months]. *Jurnal Ners*, 11, pp. 170-175.

- Rahayu, T. B. & Nurindahsari, Y. a. W. 2018. Peningkatan status gizi balita melalui pemberian daun kelor (*Moringa oleifera*) [Improving the nutritional status of toddlers through the provision of *Moringa oleifera* leaves]. *Jurnal Madani Medika*, 9, pp. 87-91.
- Reddy, V. S., Palika, R., Ismail, A., Pullakhandam, R. & Reddy, G. B. 2018. Nutrigenomics: Opportunities & challenges for public health nutrition. *The Indian journal of medical research*, 148, pp. 632.
- Rodríguez-Cruz, M. & Serna, D. S. 2017. Nutrigenomics of ω -3 fatty acids: Regulators of the master transcription factors. *Nutrition*, 41, pp. 90-96.
- Rosha, B. C., Sari, K., Sp, I. Y., Amaliah, N. & Utami, N. 2016. Peran intervensi gizi spesifik dan sensitif dalam perbaikan masalah gizi balita di Kota Bogor [The role of specific and sensitive nutrition interventions in improving nutrition problems for children under five in Bogor City]. *Buletin Penelitian Kesehatan*, 44, pp. 127-138.
- Saini, R., Manoj, P., Shetty, N., Srinivasan, K. & Giridhar, P. 2014. Dietary iron supplements and *Moringa oleifera* leaves influence the liver hepcidin messenger RNA expression and biochemical indices of iron status in rats. *Nutrition Research*, 34, pp. 630-638.
- Saini, R. K., Sivanesan, I. & Keum, Y.-S. 2016. Phytochemicals of *Moringa oleifera*: a review of their nutritional, therapeutic and industrial significance. *3 Biotech*, 6, pp. 203.
- Sedgh, G., Herrera, M. G., Nestel, P., El Amin, A. & W. Fawzi, W. 2000. Dietary vitamin A intake and nondietary factors are associated with reversal of stunting in children. *The Journal of nutrition*, 130, pp. 2520-2526.
- Shekar, M., Kakietek, J., D'alimonte, M. R., Rogers, H. E., Eberwein, J. D., Akuoku, J. K., Pereira, A., Soe-Lin, S. & Hecht, R. 2017. Reaching the global target to reduce stunting: an investment framework. *Health policy and planning*, 32, pp. 657-668.
- Shija, A. E., Rumisha, S. F., Oriyo, N. M., Kilima, S. P. & Massaga, J. J. 2019. Effect of *Moringa Oleifera* leaf powder supplementation on reducing anemia in children below two years in Kisarawe District, Tanzania. *Food science & nutrition*, 7, pp. 2584-2594.
- Soetjningsih, D. 1995. Tumbuh kembang anak [Child growth and development]. *Jakarta: Penerbit Buku Kedokteran EGC*, 1, pp. 995.
- Stefano, P., Ivana, M., Arianna, G., Letizia, Z., Angelo, G., Rosella, C., Roberta, B., Vittorio, C., Antonella, C. & Maurizio, M. 2019. Identification of microRNAs and relative target genes in *Moringa oleifera* leaf and callus. *Scientific reports*, 9, pp. 1-14.
- Susanto, H., Hernowati, T. E. & Indra, M. R. Efficacy of *Moringa oleifera* Leaf Powder as Nutrigenomic Therapy Against Malnutrition and Metabolic Perturbation Related Diseases: a Preliminary Study of Madura Islands Variety. 1st International Conference in One Health (ICOH 2017), 2017. Atlantis Press.
- Swarinastiti, D., Hardaningsih, G. & Pratiwi, R. 2018. *Dominasi Asupan Protein Nabati Sebagai Faktor Risiko Stunting Anak Usia 2-4 Tahun [The dominance of vegetable protein intake as a risk factor for stunting in children aged 2-4 years]*. *Jurnal Kedokteran Diponegoro*, 7, pp. 1470-1483.
- Teshome, B., Kogi-Makau, W., Getahun, Z. & Taye, G. 2009. Magnitude and determinants of stunting in children underfive years of age in food surplus region of Ethiopia: the case of west gojam zone. *Ethiopian Journal of Health Development*, 23.
- Valko, M., Izakovic, M., Mazur, M., Rhodes, C. J. & Telser, J. 2004. Role of oxygen radicals in DNA damage and cancer incidence. *Molecular and Cellular Biochemistry*, 266, pp. 37-56.

- Wang, Y., Gao, Y., Ding, H., Liu, S., Han, X., Gui, J. & Liu, D. 2017. Subcritical ethanol extraction of flavonoids from *Moringa oleifera* leaf and evaluation of antioxidant activity. *Food chemistry*, 218, pp. 152-158.
- World Health Organization, W. 2015. *World health statistics 2015*, World Health Organization.
- Zhang, Z. & Chandola, T. 2017. P17 Chronic malnutrition in early life and cognitive outcome in mid-childhood: evidence from four developing countries. *J Epidemiol Community Health*, 71 (Suppl 1), pp. A2-A96.
- Zongo, U., Zoungrana, S. L., Savadogo, A. & Traoré, A. S. 2013. Nutritional and clinical rehabilitation of severely malnourished children with *Moringa oleifera* Lam. leaf powder in Ouagadougou (Burkina Faso). *Food and Nutrition Sciences*, 4, pp. 991-997.