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Review Article

Immunonutrition and Hepatoprotectant Aspects of *Moringa Oleifera* Leaf Nanoemulsion Syrup as an Antituberculosis Adjuvant for Children with Tuberculosis

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ABSTRACT

Tuberculosis in children is a global health problem that decreases the quality of life of children. Based on data from the Indonesian Ministry of Health in 2016, nearly 69.000 children had tuberculosis and the case keeps increasing every year. *Moringa oleifera* leaf nanoemulsion syrup has immunonutrition and hepatoprotectant effects in children with tuberculosis. *Moringa oleifera* leaf nanoemulsion syrup contains proteins, micronutrients, and minerals which have a biological role as an immunity agent and prevent toxic effects of tuberculosis drugs. Until now, the use of *Moringa oleifera* leaf nanoemulsion syrup has been carried out for the immunomodulatory and hepatoprotective aspects. Immunomodulatory and hepatoprotective aspects will be discussed further in this literature review. The sources of articles in this literature review are pubmed.com, ncbi.com, plosone.com, sciencedirect.com, and googleschoolar.com from 2010-2020, except when there is no new research against the article. The authors searched for the keywords: "immunonutrition", "tuberculosis in children", "hepatoprotectant", and "*Moringa oleifera*". As an immunomodulator, *Moringa oleifera* leaf nanoemulsion syrup stimulate activation of polimorphonuclear (PMN) cells. As a hepatoprotectant, *Moringa oleifera* leaf nanoemulsion syrup work by reducing the side effects of conventional tuberculosis drugs such as rifampicin by suppressing the action of cytochrome p450 (CYP1A2 and CYP2B), thus decreases the production of toxic hydrazine which causes liver toxicity in tuberculosis patient. Seeing the various interests in the immunomodulatory and hepatoprotective aspects, *Moringa oleifera* leaf nanoemulsion syrup can be used as an adjuvant therapy in overcoming tuberculosis in children by stimulating the activation of immunity cell such as PMN, increasing nutrient absorption, and suppressing the action of cytochrome p450 (CYP1A2 and CYP2B).

INTRODUCTION

Tuberculosis is a tropical infectious disease caused by *Mycobacterium tuberculosis* (Zarb et al. 2012). Until now, tuberculosis has become one of the highest infectious diseases in the world with increasing mortality rate. Indonesia is the third rank on the highest number of tuberculosis cases and it is estimated that the mortality rate in 2020 reach around 1.4 million people (Buonsenso et

al. 2021). Tuberculosis cases not only attacked adult population but also children. According to the data from the Indonesian Ministry of Health in 2016, nearly 69.000 children aged 0-15 years old had tuberculosis and nearly 95% of patients come from the middle to lower socio-economic groups (Kemenkes RI 2016b).

Children in their early development phase (golden period) are susceptible to tuberculosis infection due to the lack of cellular immunity (vanden Driessche et al. 2013). Currently, the main solution in preventing tuberculosis is using the Bacille Calmette – Guérin (BCG) vaccination which is a mandatory vaccine from an early age (Davenne & McShane 2016). Immunity provided by BCG vaccination is a nonspecific immunity of up to 80% so that some children are still able to become infected with tuberculosis in the future (WHO 2017). If children are left infected from childhood and do not get proper care, it will decrease the quality of the nation's future human resources due to high morbidity (Aggarwal 2019).

Current treatment for pediatric tuberculosis is carried out according to standards guidelines with a long duration of drug administration around 2-3 months in the form of crushed tablets. It makes the children less obedient to take the antituberculosis drugs (Munawarah et al. 2019). In addition, the consumption of antituberculosis drugs is known to cause hepatotoxicity (Sanchez-Codez et al. 2020). A safer method of treatment is needed for children with tuberculosis. One potential therapeutic method is using herbal medicine, such as *Moringa oleifera* leaf (Abd elhameed et al. 2018).

Moringa oleifera is a plant that has a cultural-medical-magical aspect and is easily found in Indonesia, and rarely used as an economic commodity (Kasolo et al. 2010). This plant is often called "nutritional dynamite" in Europe and America since it contains phytochemicals that have many functions as antioxidants, painkillers (analgesics), and immunostimulants (Stohs & Hartman 2015). Research conducted *in vitro* in Nigeria stated that the use of *Moringa oleifera* leaf showed antibacterial potential because unsaturated fatty acids have an inhibitory power to prevent bacterial growth by directly causing lysis of bacterial cells and preventing electron transport in oxidative phosphorylation (Kasolo et al. 2010). Beside the potency as antibacterial, antioxidant, immunostimulant, and analgesic, *Moringa oleifera* as a traditional potential medicine also has potency as antidiabetic, anti infertility, antiinflammatory, anticancer, and antiarthritis (Sahoo et al. 2015).

Adjuvant administration in the form of *Moringa oleifera* leaf nanoemulsion syrup can be given in line with the medicines given by the doctor if the child has been confirmed as an active tuberculosis patient (Harausz et al. 2018). The pathophysiological process of tuberculosis in children has a latent phase and it is diagnosed before the primary or gohn complex is formed (Delgado & Bajaj 2019). When the complex is formed, it will only cause clinical manifestations in the form of redness or induration of the skin which is called a positive tuberculin test (Aggerbeck et al. 2018). The tuberculin test began to mark its clinical course on the third day when it became infected,

this event indicated that the cellular immunity process had formed specific antibodies against *Mycobacterium tuberculosis*. In addition, based on the progressive pathophysiological process, tuberculosis in children will lead to impaired nutritional status so that they are prone to triggering malnutrition (Hoyt et al. 2019). These impaired nutritional status in children continue to increase, along with the prevalence of tuberculosis in children that also continues to increase (Kemenkes RI 2016a). According to WHO, there are 50.000 cases that are not reported every year. This shows that there are many undetected tuberculosis cases in children that need to be treated (WHO 2014).

Starting from the condition of the positive tuberculin test results, the adjuvant supplementation of *Moringa oleifera* leaf nanoemulsion syrup which has been added with glucose or sucrose type (which also functions as a natural preservative) can be given to children along with the administration of antituberculosis drugs which tend to be bitter (Pal et al. 2011). The administration of nanoemulsion syrup from *Moringa oleifera* leaf also contains protein and micronutrients which help to improve drug function because children with tuberculosis tend to become weak and experience weight loss (Leone et al. 2015).

The preparation of nanoemulsion from *Moringa oleifera* leaf is extracted using 96% ethanol by maceration technique (Puspitasari & Proyogo 2017). By adding maltodextrin with the *Moringa oliefera* leaf extract, it will increase its solubility and can be used as a carrier to protect secondary metabolites in *Moringa oleifera* (Jusnita & Tridharma 2019). The nanoemulsion of *Moringa oleifera* will increase absorption in the digestive mucosa (Nkya et al. 2014). This nanoemulsion will increase the antioxidant effect in *Moringa oleifera* leaf (Wright et al. 2017). The use of nanoemulsion is to improve the *Moringa oleifera* potency as an antituberculosis adjuvant in children because it increases the absorption capability of the patient's intestinal mucosa (Jusnita & Tridharma 2019).

Therefore, the use of *Moringa oleifera* leaf is a better choice because it is a tropical plant that is relatively easy to cultivate (Leone et al. 2015). The abundant number of ingredients that are rarely known to the public and their various mechanisms make *Moringa oleifera* leaf in the form of nanoemulsion syrup such a promising modality in the co-management of tuberculosis in children (Famewo et al. 2017).

MATERIALS AND METHODS

The source of articles in this literature review is collected using search engines: pubmed.com, ncbi.com, plosone.com, sciencedirect.com, and googleschoolar.com.The authors searched for the keywords "immunonutrition","tuberculosis in children", "hepatoprotectant", and "*Moringa oleifera*". We selected the proceeding or journal in Indonesian or English. Furthermore, it is carried out by reading and understanding the abstract and article content. The inclusion criteria were all research articles concerning the

relationship of nutrition in *Moringa oleifera* with tuberculosis in children. Articles from 2010-2020 are included, except when there is no new research against the article. Of the 130 articles that were reviewed, only 63 articles were suitable as references.

RESULTS AND DISCUSSION

Immunopathology Concept of Tuberculosis in Children

Transmission of tuberculosis in children is often as a result of staying at home. At home, children tend to have close contact with an active tuberculosis family member (Aristoff et al. 2010). Tuberculosis in children is generally primary tuberculosis which is a tuberculosis infection characterized by a positive tuberculin skin test (Hunter 2016; Ter Beek et al. 2019; Starke 2020).

Mycobacterium tuberculosis is transmitted when its 1-5 µm droplet nuclei are aerosolized from patients with pulmonary or laryngeal tuberculosis and are inhaled into the alveoli. The first process begins with innate immunity by alveolar macrophages and dendritic cells that activate phagocytosis process of *Mycobacterium tuberculosis*. Furthermore, it will trigger the activation of the complement pathway, stimulate the production of proinflammatory cytokines in the form of interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). It also increases the opsonization as the first introduction of germs into the body and phagocytosis to control the infection that occurs. This opsonization causes the body to generate a second body defense response called adaptive immune response. The adaptive immune response induces T cells, such as T helper (Th)-1 CD4+ T cells, CD8+ cytotoxic T cells, and gamma delta (γδ) T cells which then trigger the secretion of cytokines that control the growth of *Mycobacterium tuberculosis* (Thomas 2019).

In children, their immunity has not yet matured, so it will be difficult to control the growth of *Mycobacterium tuberculosis*, thus triggering severe inflammation that will invade the lung parenchyma (Thomas 2019). Infants and neonates are at higher risk due to the absence of production and function of toll-like receptors (TLRs), dendritic cells, and macrophages, as well as deficiency of CD4+ function to express Th1. This weak immune system makes children, especially babies and neonates, are highly susceptible to tuberculosis infection. Tuberculosis tends to put children in a state of progressive weight loss. This surely leads to chronic inflammation and malnutrition in children (Koethe & von Reyn 2016; Ter Beek et al. 2019) (Figure 1).

Tuberculosis patients often experience heavy weight loss. The compound that plays a role in body weight regulation is leptin. The inflammation that occurs in tuberculosis which causes the increase of TNF-α will reduce leptin levels. Leptin is important because it is related to Cell-Mediated Immunity (CMI). If the levels of leptin are low, it contributes to the decline in T cell function (Van Crevel et al. 2002). The decreasing of T cell function reduces the production of type 1 cytokines. The examples of type 1 cytokines

are anti-inflammatory interleukin-2 (IL-2) and IFN-γ which are the main mediators of immunity and increase disease progression. Tuberculosis will also increase energy expenditure which leads to conditions of weight loss or wasting that lead to cachexia (Van Crevel et al. 2002; Chandrasekaran et al. 2017).

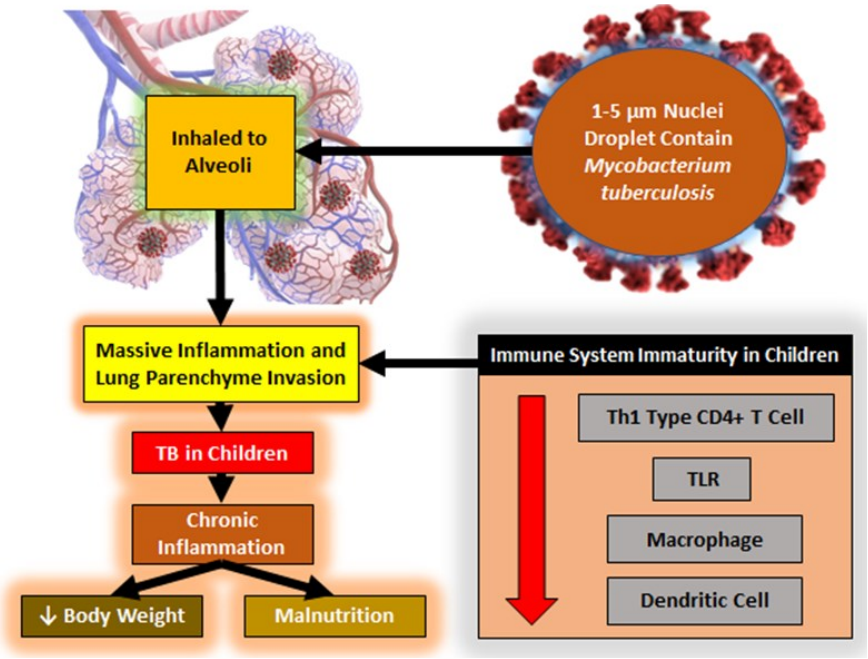

Figure 1. Pathogenesis of Tuberculosis in Children (Pal et al. 2011; Leone et al. 2015). (The red down arrow in "Immune System Immaturity in Children" box indicates 'decreasing'; TB = tuberculosis, TLR = toll-like receptor).

Decreased appetite resulted in protein energy malnutrition (PEM) has a direct effect on the work of T-cells. Severe PEM triggers atrophy of the thymus and peripheral lymphoid organs, then it triggers leukopenia, a decrease in the CD4/CD8 ratio, and increases immature T cells in peripheral blood. Protein deficiency also reduces the expression of CD25 and CD27, the molecules for the activation and proliferation of T cells. Under malnutrition conditions, there can be interference with complement factor C3 opsonization and the ability of phagocytes to kill pathogens. In addition, various antigen-presenting cells (APCs), such as B lymphocytes, macrophages, dendritic cells, and Kupffer cells will decrease in number if they are malnourished (Chandrasekaran et al. 2017) (Figure 2).

The Role of *Moringa oleifera* Leaf Nanoemulsion Syrup in Imunonutrition

Moringa oleifera leaf nanoemulsion syrup has a number of macronutrients such as vegetable protein also micronutrients such as vitamins, minerals, as well as trace elements which are associated with immunomodulatory effects against intracellular pathogens such as *Mycobacterium tuberculosis* (Chandrasekaran et al., 2017). Nfambi et al. (2015) tested the administration of *Moringa oleifera* methanol extract against hematological parameters in an *in vivo* study and found an increase in several parameters, especially leukocytes that play an important role in immunity compared to immunocompromised mice without

Moringa oleifera administration (Kant et al. 2015; Nfambi et al. 2015).

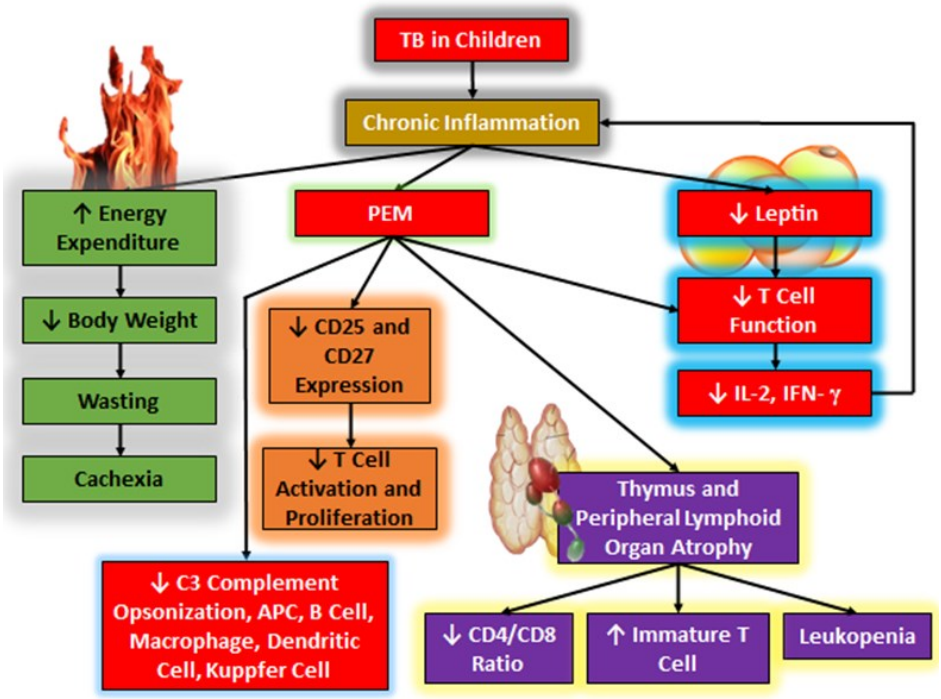

Figure 2. Pathogenesis of Tuberculosis Complication in Children (Pari & Kumar 2002; Tostmann et al. 2008; Wright et al. 2017). (↑ = increasing; ↓ = decreasing; TB = tuberculosis; PEM = protein energy malnutrition; CD = cluster of differentiation; APC = antigen presenting cell; IL = interleukin; IFN = interferon).

Moringa oleifera has potency as an immunomodulator because it contains prebiotics (Alabi et al. 2017). Prebiotics are dietary products rich in fiber that provide a food source for the normal bacterial flora present in the intestines (La Fata et al. 2017). These prebiotics will be fermented by the normal intestinal flora bacteria to produce short-chain fatty acids (SCFAs) as a by-product (Goyal et al. 2020). These SCFAs are very easily absorbed by the body (Feng et al. 2018). While absorbing, this prebiotic triggers the colonization of good bacteria in the intestine such as *Lactobacillus* sp. and *Bifidobacterium* sp. which suppress the presence of bad bacteria such as *Salmonella* sp. and *Campylobacter* sp. (Hemalatha et al. 2017; Feng et al. 2018; Kim et al. 2019). Prebiotics also affect the lungs and can be explained by the theory of the gut-lung axis, in which a healthy intestinal condition will impact the health of other organs, like lung. This is because prebiotics will be assimilated by gut microbiote and it produces SCFAs metabolite and stimulates the migration of immune cell to distal organ such as lung (Zhang et al. 2020). SCFAs as a result of prebiotic metabolism by normal intestinal flora bacteria contained in *Moringa oleifera* can modify the intestinal environment by increasing the good bacteria and thereby increasing nutrient absorption (Al-Sheraji et al. 2013). The increase of nutrient absorption will increase the children weight. In addition, SCFAs have an antidiarrheal effect and do not trigger lactose intolerance, making them safe for children (Goyal et al. 2020) (Figure 3).

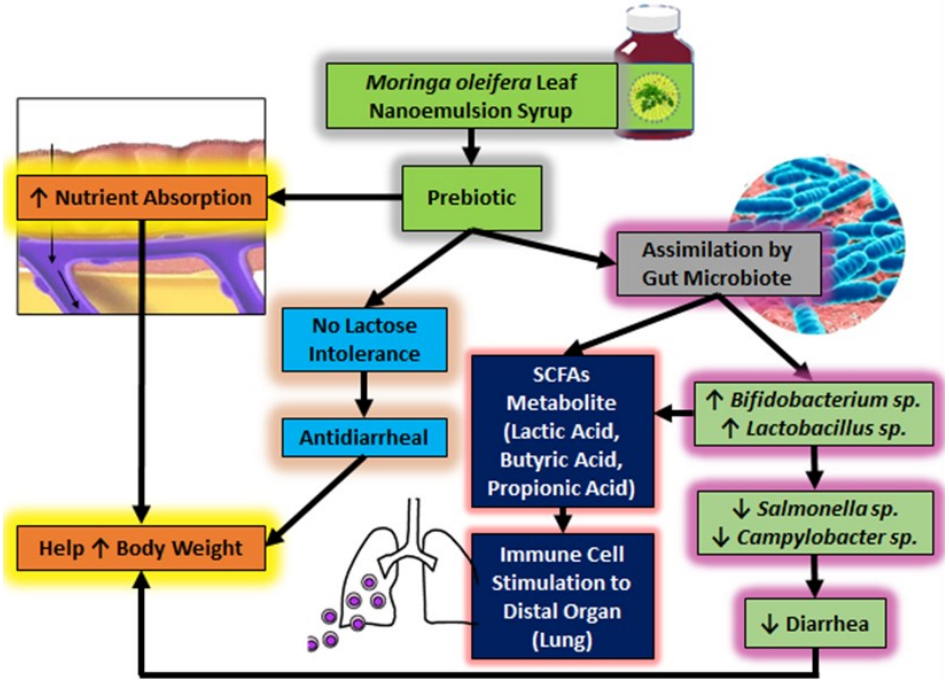

Figure 3. Mechanism of Action of Prebiotic from *Moringa oleifera* Leaf Nanoemulsion Syrup in Immunonutrition Aspect (Al-Sheraji et al. 2013; Alabi et al. 2017; la Fata et al. 2017; Hemalatha et al. 2017; Feng et al. 2018; Kim et al. 2019; Goyal et al. 2020; Zhang et al. 2020).

Low leptin in children with tuberculosis is due to chronic inflammation. Therefore, leptin administration could have a positive impact on tuberculosis patients because it would increase CMI. However, this is not feasible if it is done in Indonesia because there are no leptin drugs available in Indonesia (van Crevel et al. 2002). Because there are no leptin drugs available in Indonesia, thus a traditional potent herbal medicine application, such as *Moringa oleifera* leaf nanoemulsion syrup had an appetite-enhancing or orexigenic effect from zinc and vitamin E may result in statistically significant weight gain in animal studies (van Crevel et al. 2002; Uwaifo 2020).

Vegetable protein contained in *Moringa oleifera* leaf nanoemulsion syrup has the effect of increasing the CD4/CD8 ratio, IL-2, IFN-γ, and expression of CD25 as well as CD27. This increases the patient immunity by increasing the body natural response of microbial infection by differentiating between foreign body such as bacteria and "self" cell in the body (Chandrasekaran et al. 2017).

Various trace elements contained in *Moringa oleifera* leaf nanoemulsion syrup, such as zinc, copper, and iron have benefits in the treatment of tuberculosis. Zinc and copper can strengthen the innate immune response which acts on the phagolysosome. The more its concentration in the phagolysosome, the better its bactericidal effect (Djoko et al. 2015). Iron may increase antimicrobial function by increasing the production of IL-4, IL-10, IL-5, and Forkhead Box P3 (FOXP3). Activation of FOXP3 increases the function of T cells (Chandrasekaran et al. 2017).

Various minerals are also present in the nanoemulsion syrup from *Moringa oleifera* leaf, one of which is calcium. Calcium is needed by the macro-

phages because it requires concentration ten times higher to fight tuberculosis than without tuberculosis (Chandrasekaran et al. 2017).

Various vitamins are also contained in *Moringa oleifera* leaf nanoemulsion syrup, such as vitamins A, B6, C, and E. Vitamin A increases cellular and lymphoproliferative immune response. Meanwhile, vitamin B6 increases the activity of natural killer (NK) cells and lymphocytes. Vitamin C reduces ROS and thus reducing tissue damage caused by tuberculosis. Vitamin E reduces oxidative stress and improve T cell function (Chandrasekaran et al. 2017) (Figure 4).

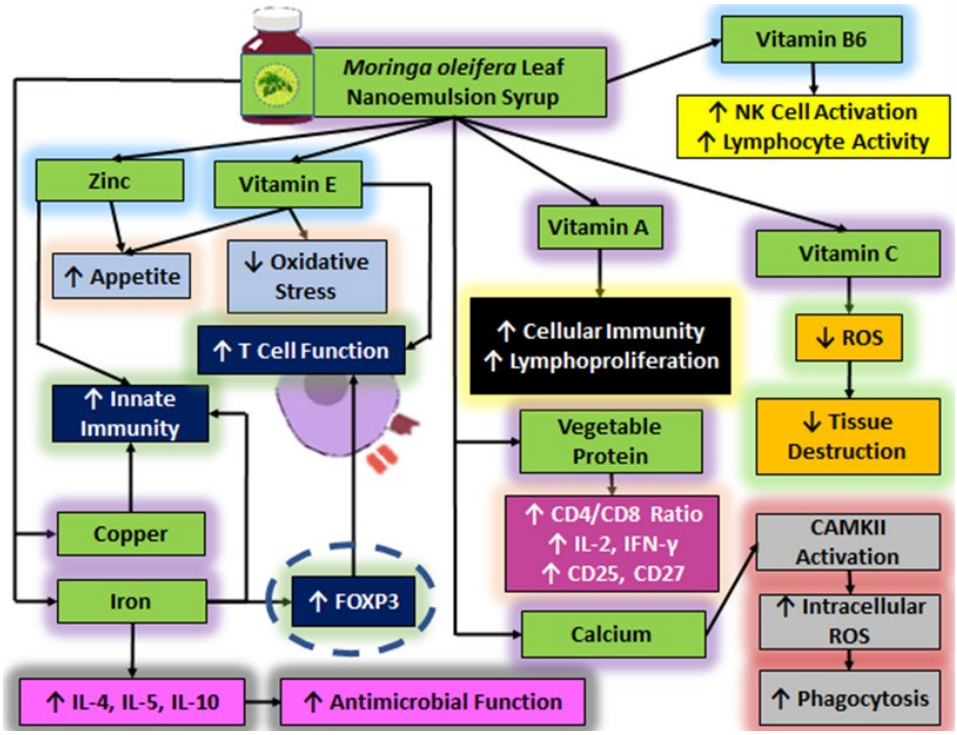

Figure 4. Mechanism of Action of Macronutrient and Micronutrient from *Moringa oleifera* Leaf Nanoemulsion Syrup in Immunonutrition (van Crevel et al. 2002; Djoko et al. 2015; Nfambi et al. 2015; Chandrasekaran et al. 2017; Uwaifo 2020). (ROS = reactive oxygen species; CAMKII = Ca^{2+}/CAM-dependent protein kinase II; IL = interleukin; IFN = interferon; CD = cluster of differentiation; FOXP3 = Forkhead Box P3; NK = Natural Killer).

Pathophysiology of Antituberculosis Drug-Induced Hepatotoxicity

Antituberculosis drugs have been reported to have toxicity to the liver via cytolytic mechanisms that damage membranes and organelles through degradation of phospholipids (Pari & Kumar 2002; Tostmann et al. 2008; Abd el-hameed et al. 2018; Mangwani et al. 2020). In general, antituberculosis drugs have side effects on the liver because they contain toxic metabolites, reactive oxygen species (ROS), and free radicals (Jia et al. 2019). In addition, antituberculosis drugs also activate CYP2E1 thereby increasing fatty acid accumulation and LDL uptake. All of these will contribute to liver damage (Mangwani et al. 2020).

Antituberculosis drugs that contribute to liver toxicity include: isoniazid (INH), RIF, and pyrazinamide (PZA) (Mangwani et al. 2020). INH

causes liver toxicity by increasing the production of toxic compound called acetyl hydrazine (Chan et al. 2017; Mangwani et al. 2020). RIF can increase INH metabolism and produce toxic intermediates such as hydrazine through the INH hydrolase enzyme (Pari & Kumar 2002; Wang et al. 2016). In addition, RIF can also impair membrane permeability, thereby impairing glucose-6-phosphate activity. This leads to high lipid peroxidation in the liver which has a negative effect on liver enzymes (Shehu et al. 2017). PZA causes liver toxicity by increasing the production of 5-hydroxypyrazinoic acid which has a toxic effect on the liver (Mangwani et al. 2020).

Moringa oleifera Leaf Nanoemulsion Syrup as Hepatoprotectant

Some compounds from *Moringa oleifera* leaf such as beta carotene, alkaloids, flavonoids, glycosides, saponins, tannins, and terpenoids can repair damage of the liver cells and improve the function of the SGOT, SGPT, and ALP enzymes (Pari and Kumar 2002; Mangwani et al. 2020). These compounds also have a hepatoprotective effect by reducing levels of lipid peroxidation markers such as thiobarbituric acid reactive substances (TBARS) and hydroperoxides through increased glutathione peroxidase (GPx) by kaempferol. This *Moringa oleifera* leaf nanoemulsion syrup can improve hepatic cell structure by increasing phospholipid levels (Pari & Kumar 2002; Abd elhameed et al. 2018). Decreased malondialdehyde (MDA) and tumor necrosis factor-alpha (TNF-α) as well as increased adiponectin were also identified in *in vivo* studies. This adiponectin later activates AMP-activated kinase and peroxisome proliferator-activated receptor alpha (PPAR-α) which suppress TNF-α and trigger IL-10. In addition, adiponectin also suppresses the proliferation and migration of hepatic stellate cells by binding to adipore-ceptor-2 thus suppressing hepatic fibrosis (Abd elhameed et al. 2018). These compounds also reduce serum bilirubin so that the symptoms of jaundice can be minimized. Phytochemicals compound such as glucosinolates contained in the *Moringa oleifera* leaf nanoemulsion syrup also suppresses the action of cytochrome p450 (CYP1A2 and CYP2B) (Mishra et al. 2011; Mangwani et al. 2020). This causes RIF, which is an inducer of the p450 pathway as previously described, inhibits INH metabolism, thus decreases the production of toxic hydrazine (Mangwani et al. 2020).

SCFAs are one of the products of prebiotic metabolism contained in the *Moringa oleifera* leaf nanoemulsion syrup. These SCFAs can improve cir-rhosis of the liver (Goyal et al. 2020) (Figure 5).

Moringa oleifera leaf at the dose of 1000 mg/kgBW was more effective than silymarin and showed significant differences in the groups that were given only RIF and INH to test its different potency for treating liver disease. Compared with *Moringa oleifera,* silymarin is a well-known plant that has been clinically used since 2000 years ago as a plant for treating liver disease. *Moringa oleifera* also showed a decrease in MDA and TNF-α (as a proinflammatory marker), and also a dose-dependent increase in GPx and adiponectin (as an antioxidant and antiinflammatory marker). In addition,

Moringa oleifera is known to increase RIF concentration in plasma, allowing reduction of the dose and duration of antituberculosis drugs (Abd elhameed et al. 2018; Chandra Dinda 2017).

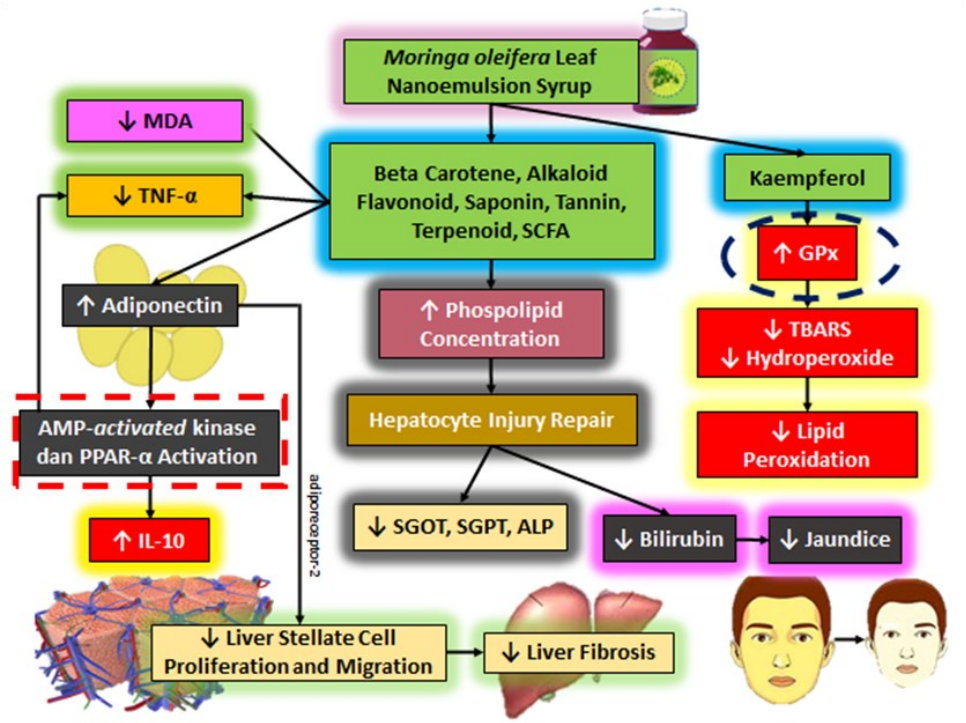

Figure 5. Mechanism of Action of Secondary Metabolites and SCFA from *Moringa oleifera* Leaf Nanoemulsion Syrup as Hepatoprotectant) (Pari & Kumar 2002; Mishra et al. 2011; Abd elhameed et al. 2018; Goyal et al. 2020; Mangwani et al. 2020) (MDA = malondialdehyde; TNF = tumor necrosis factor; AMP = adenosine monophospate; PPAR = peroxisome proliferator-activated receptors; IL = interleukin; SCFA = short-chain fatty acids; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ALP = alkaline phosphatase; GPx = glutathione peroxidase; TBARS = thiobarbituric acid reactive substances).

The Advantages of *Moringa oleifera* Leaf Nanoemulsion Syrup as an Adjuvant Agent in Children with Tuberculosis

The advantages of *Moringa oleifera* leaf nanoemulsion syrup can be seen from several aspects, such as the form of nanoemulsion syrup, various efficacies of the *Moringa oleifera* leaf and the economic potential of this modality.

The packaging of the drug in the form of nanoemulsion syrup aims to increase the compliance of the patient. This is because *Moringa oleifera* that is packaged in other forms like powder may induce a bitter taste and thereby can reduce the patient compliance. In addition, the form of nanoemulsion syrup also increases the absorption of the *Moringa oleifera* (Tayeb & Sainsbury 2018; Harwansh et al. 2019; Nakano et al. 2019).

Moringa oleifera leaf is known to be beneficial against tuberculosis because it is rich in nutrients, a hepatoprotectant agent, and may enhance the actions of rifampicin (RIF bio-enhancer). *Moringa oleifera* contains four times of calcium in milk, seven times of vitamin C in oranges, three times of potas-

sium in banana, three times of iron in spinach, four times of vitamin A in carrot, and two times of protein in milk (Moyo et al. 2011). Children nutritional status must be taken as consideration in the management of tuberculosis in children, therefore giving *Moringa oleifera* as an adjuvant is very compatible because it is rich in nutrients and may increase the children appetite (Uwaifo 2020).

Previous studies found that *Moringa oleifera* can induce hepatoprotective effect significantly (Buraimoh et al. 2011; Pari & Kumar 2002; Saalu et al. 2011). The administration of *Moringa oleifera* was able to reduce the level of serum AST and ALT which was previously high due to the administration of anti-tuberculosis drugs (INH and RIF). This mechanism is caused by the activity of anti-lipid peroxidase induced by *Moringa oleifera*, resulting in the improvements of the plasma membrane and liver structural tissue (Abd elhameed et al. 2018). In addition, *Moringa oleifera* also plays a role as a bio-enhancer for RIF. *Moringa oleifera* is able to inhibit cytochrome P450 which acts in the process of RIF metabolism. This inhibition leads to the increase of RIF concentration in the plasma (Pal et al. 2011). This allows reduction of the dose and timing of therapy and may reduce the risk of drug toxicity. To date, there are no studies that found the side effects of *Moringa oleifera* both in humans and experimental animals. *Moringa oleifera* has been consumed traditionally by people especially in Indonesia, therefore making it is such a safe drug for consumption (Stohs & Hartman 2015).

Previous study found that the content of *Moringa oleifera* is different in that plant domestically compare to that live in the wild (Chodur et al. 2018). *Moringa oleifera* leaf nanoemulsion syrup can also be consumed directly, cooked, or stored for months without using refrigerator and still provide the same nutritional value (Mary 2015). When compared with other conditions, giving *Moringa oleifera* is also very beneficial because *Moringa oleifera* continue to grow during the dry season when other food sources are usually scarce.

The Limitations of *Moringa oleifera* Leaf Nanoemulsion Syrup as an Adjuvant Agent in Children with Tuberculosis

The main limitation is *Moringa oleifera* leaf nanoemulsion syrup only can be the adjuvant for the conventional antituberculosis drugs for some aspects of tuberculosis patophysiology. Another limitation is the lack of comprehensive and detailed mechanism of action from compound in *Moringa oleifera* such as why kaempferol increase GPx. This encourages the need for an integrated research on *Moringa oleifera* against tuberculosis in children.

CONCLUSION

Based on the review that has been done, *Moringa oleifera* leaf nanoemulsion syrup is a potential adjuvant agent in the management of children with tuberculosis. The immunonutrition and hepatoprotectant mechanism induced by *Moringa oleifera* as well as the form of nanoemulsion syrup is a suitable form of drug for children by stimulating the activation of immunity cell such as

PMN, increasing nutrient absorption, and suppressing the action of cytochrome p450 (CYP1A2 and CYP2B). Further research on *Moringa oleifera* at preclinical and clinical levels are needed to fully understand and explore the role of *Moringa oleifera* in the management of tuberculosis in children.

AUTHORS CONTRIBUTION

N.B.W.S. designed the research, colleted and analyzed the data, and wrote the manuscript. A.I.Y.D.P. collected and analyzed the data. M.I.D.S. wrote the manuscript. A.W.I. designed the research and wrote the manuscript. I.A.I.W. provided language help and writing assistance.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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