Chapter

Potential Natural Product from Tropical Fruits: A Mixture Young Coconut Fruit and Kaffir Lime Fruit as Immunonutrition for the Treatment of Sepsis by Lipopolysaccaride *Escherichia coli* (Infectious Disease)

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Abstract

The high number of cases reported of antibiotic resistance use and mortality due to gram-negative sepsis, triggered the development of natural agents to be used in the prevention and treatment of sepsis. Studies continue to be developed on the use of tropical fruits such as coconut fruit and kaffir lime fruit which contain high antioxidants and many potential compounds. Recent experimental data has proven that the high antioxidant activity found in the coconut fruit mixture, namely processed fruit flesh and coconut water and added kaffir lime juice, can be used as an immunonutrition agent that can improve body physiology and can increase the survival rate of test animals from endotoxemia lipopolysaccharide induced by Eschercia coli intraperitoneally. This chapter provides an overview of the potential of natural products that can be used as immunonutrition preparations. Finally, this provides information showing the importance of the intake of immunonutrition in conditions of sepsis infection.

Keywords: sepsis, natural product, immunonutrition, coconut fruit, kaffir lime

1. Introduction

Infectious diseases are diseases caused by the entry of one of four types of microbes, namely viruses, bacteria, protozoa or fungi that are harmful (pathogens). Of the millions of types of microbes that exist, only about 1,400 are pathogenic in humans, but critically only 150 have the ability to transmit from human to human and have the potential to cause epidemics [1].

Sepsis is a severe infection, and when the body is exposed to infection it will affect all organs of the body and many organs can affect it. Infection can come from the respiratory cavity, digestive tract, and wounds. When the human immune

system drops, the body cannot overcome the infection and the infection will circulate throughout the body so that our body will respond to inflammation to fight the bacteria cause death [2].

By definition, sepsis is divided into several conditions, namely bacteremia or fungimia, infection, sepsis, severe sepsis and septic shock [3]. Sepsis is divided into several stages based on the body's response to infection, ranging from fever and leukocytosis to hypotension and impaired function of several organs [4]. Although almost any microorganism can be associated with sepsis and septic shock, the most common pathogenic etiologies are gram-positive bacteria (40%): *Staphylococcus aureus*, *Streptococcus pneumoniae*, Staphylococcus coagulase negative, and Enterococcus. Meanwhile, gram-negative bacteria (38%): *Escherichia coli* and *Pseudomonas aeruginosa* were the most frequently isolated bacteria in sepsis [3].

The biggest cause of sepsis is gram-negative bacteria (−) with a percentage of 60–70% of cases being the main cause of death in intensive care units, although antibiotics are new, mortality due to gram-negative sepsis remains high. This is because gram-negative bacteria tend to be more resistant to antimicrobial agents than gram-positive bacteria, due to the additional protection provided by the outer membrane [5]. This is why antibiotic resistance is now a public health problem worldwide involving a broad spectrum of microorganisms and different classes of antibiotics, including multidrug-resistant bacteria [6]. Therefore, it is very important to find new drugs to overcome this problem.

Sepsis infection produces various products that can stimulate immune cells. These cells will be stimulated to release inflammatory mediators. The product that plays an important role in sepsis is lipopolysaccharide (LPS). LPS or endotosin glycoprotein complex is the main component of the outer membrane of gram-negative bacteria. Lipopolysaccharides stimulate tissue inflammation, fever and shock in infected patients [7].

Sepsis is also defined as an irregular host response caused by infection and associated with severe microvascular, hemodynamic, metabolic, endocrine, and immune disorders, causing life-threatening organ dysfunction, characterized by a severe inflammatory response to systemic infection caused by pathogenic microorganisms. In severe cases, sepsis can lead to death with multiple organ failure as the main cause [7]. The catabolic response during acute sepsis severely depletes the body's nutritional resources, generates large amounts of cellular waste products and is in dire need of adequate nutrition [8].

Sepsis is characterized by early massive catabolism, loss of lean body mass and increased hypermetabolism that lasts for months to years. Insufficient nutrition and immune dysfunction did not have a synergistic effect on mortality in critically ill septic patients but it is expected that well-fed patients with normal immune function have the best chance of survival. Immunocompetent patients who are undernourished have the worst prognosis. Early nutrition should seek to correct micronutrient/vitamin deficiencies, provide adequate protein and moderate non-protein calories and well-nourished patients produce endogenous energy [9].

From a pathophysiological perspective, sepsis is often regarded as a syndrome that progresses from an initial inflammatory and hypermetabolic state to a more protracted state, characterized by lymphocyte exhaustion, apoptosis, and reduced capacity of monocytes and macrophages to release pro-inflammatory cytokines and trigger secondary infection [10] and cellular metabolic processes undergo fundamental changes without returning to normal homeostasis [11]. The degree of inflammation and immune suppression varies between individuals and is determined by host-(genetic heterogeneity, age, and comorbidities), pathogen-(burden, type, and virulence), and therapy-related factors (time, adequacy) [12].

Since ancient times, humans have used plants to treat common infectious diseases and some of these traditional medicines are still included as part of the habit of treating various diseases. Chemicals from natural products facilitate a large number of several bioactive secondary metabolites that have been found to fight infectious diseases [1].

Natural products are secondary metabolites or chemical compounds produced by living organisms and which have bio-activity, can be useful against microbes originating from microorganisms that make secondary metabolites can be produced into drugs. The superiority of plants as a resource for the discovery of anti-infective drugs, and the latest technology allows a wider line of investigation. Natural plant products represent a promising and largely untapped source of new chemical entities from which new anti-infectives can be discovered [13].

2. Immunonutrition for infectius disease and sepsis

The natural defenses of the human body depend on the integrity of the immune system which is responsible for curbing the course of pathogens and their complications. The immune system is divided into two types, innate and adaptive, each of which is responsible for responding to initial and repeated infections. Both types of immune systems rely on the use of mediators such as enzymes, pro-inflammatory cytokines, antibodies, and reactive oxygen and nitrogen species to combat many disease processes. The synthesis and functionality of these mediators depend on the individual immunonutrient components [14].

Immunonutrition is the term given to nutritional interventions that regulate immune and inflammatory responses. This is done by administering a formula containing a range of immunonutrients in greater amounts than is normally found in food. Some of the more commonly used immunonutrients include arginine, glutamine, branched-chain amino acids, omega-3, 6 and 9 fatty acids, trace metals (eg zinc, copper, iron), and nucleotides or antioxidants [15, 16]. The main targets of these immunonutrients involve mucosal barrier function, cellular defenses, and local or systemic inflammation [17].

Previous research has shown a close relationship between nutritional deficiencies and impaired immune function. The correlation between malnutrition and infection is particularly pronounced in less immunocompetent groups, such as young children and the elderly, who are prone to higher rates of respiratory and gastrointestinal diseases. One study determined that enteral glutamine administration reduced the incidence of moderate to severe sepsis and pneumonia in premature infants and critically ill patients. Other studies have shown that zinc supplementation at physiological levels for 1–2 months enhances immune response, decreases the incidence of infection, and ultimately improves survival [14].

In contrast, patients who have undergone surgery, trauma, or infection may experience the deleterious effects of a prolonged systemic inflammatory response because of the greater need for metabolic and essential nutrients. They may even experience compensatory immunosuppression as a result of chronic inflammation [4]. Many studies have shown that various combinations of immunonutrients can provide appropriate metabolic support for patients experiencing complications from malnutrition associated with illness, while effectively reducing infection rates and length of hospital stay. In addition, other immunonutrients such as proteins, vitamins, trace metals, and enzymes exhibit antioxidant properties that limit the extent of tissue damage and reduce the possibility of carcinogenesis [14, 18].

Nutritional therapy refers to the administration of nutrients with certain beneficial actions (eg for antioxidant effects) specifically aimed at immune defense

mechanisms and to inhibit excessive proinflammatory responses during the catabolic phase of a disease [19, 20]. Future research on immunonutrition should be multidisciplinary and on a larger scale to further validate the great benefits of immunonutrition, while providing data on optimal mixes and doses for use in different groups of patients [17, 21, 22].

Immunonutrition therapy is an effort to reduce or eliminate potential pathogens and toxins, fulfill nutritional intake and act as antioxidants that can modulate natural and adaptive immune defense mechanisms in patients with critical illnesses such as sepsis. The concept of nutritional support in an effort to modulate immune function is known as immunonutrition (Immune-enhancing diets or Immuno-modulating diets) which is a therapeutic approach to pathological changes in adaptive and natural immunity, which arise secondary to inflammation and systemic infection through the administration of immunonutrients [23, 24]. The most relevant nutritional therapy in septic patients is the intake of the amino acids glutamine and arginine, fatty acids, selenium, and vitamin C [8].

Micronutrients are nutrients that the body needs to carry out body functions. The amount is less than 100% g per day and consists of vitamins and minerals. It cannot be synthesized in the body. Research in the United States states that the prevalence of sepsis tends to increase by 8.7% every year. In sepsis, nutrition is one of the important components that can promote the success of treatment. Micronutrients, especially fat-soluble vitamins, are toxic if the amount exceeds the body's ability to accept them. Although there are guidelines and mutual agreement on the use of sepsis, it is still necessary to pay attention to micronutrients that have the potential to have adverse effects. In the case of sepsis, micronutrients also determine the success of treatment because of the redistribution of vitamins and trace elements from circulation to tissues that play a role in protein formation and the immune system. Micronutrient supplementation is considered to reduce mortality. However, the toxicity of fat-soluble micronutrients still needs to be watched out for if the dose is excessive [25].

The role of micronutrients in metabolic processes is to maintain the function of body tissues. Hypermetabolism causes an increase in the production of Reactive Oxygen Species (ROS) as a result of an increase in oxidative metabolism that can damage cells, especially unsaturated fatty acids found in cell membranes and nucleus. Micronutrients also play a role in helping the body neutralize the negative effects of free radicals [26].

3. Young coconut fruit and kaffir lime fruit as immunonutrition for the treatment of sepsis by Lipopolysaccaride *Escherichia coli* (infectious disease) through antioxidant activity

Young hybrid coconut (*Cocus nucifera* L.) and kaffir lime (*Citrus hystrix*) contain antioxidant compounds that are used as immunonutrient agents. A study has been conducted on a test dosage form of 100 mg/kgbw/day made from a mixture of young coconuts with a concentration of 20% flesh with added coconut water and 1 ml of kaffir lime juice, assessed as having the potential to be developed as an immunonutrient agent in sepsis in mice. White male induced sepsis with *Escherichia coli* Lipopolysaccharide through the antioxidant activity of the phytonutrients contained in the test preparation. Based on the antioxidant activity test of the preparations KJ1, KJ2 and KJ3, which are test preparations added with 1 ml of kaffir lime juice, it turns out to be able to increase the antioxidant activity of the preparations when compared to preparations that are not given additional kaffir lime juice, namely preparations K1, K2 and K3. This is closely related because of the

effect of adding kaffir lime to the process of inhibiting rancidity or rancidity. The test preparation was KJ1 from 15% young coconut flesh with coconut water and 1 ml of kaffir lime juice was added. KJ2 of young coconut flesh 20% with coconut water and added 1 ml of kaffir lime juice. KJ3 from young coconut flesh 25% with coconut water and added 1 ml of kaffir lime juice. Next K1 of young coconut flesh 15% with coconut water. K2 of young coconut flesh 20% with coconut water. K3 from young coconut flesh 25% with coconut water [27].

The rancidity of processed coconut meat can be overcome by adding ingredients that contain antioxidants, one of which is kaffir lime juice. The effect of the addition of kaffir lime (*Citrus hystrix*) on the process of inhibiting rancidity or rancidity arising from the oxidation of unsaturated fatty acids contained in processed coconut meat [28].

The presence of antioxidant content in the test preparation of a mixture of meat and coconut water with the addition of kaffir lime juice is thought to act as a cofactor that plays a role in the immune response, especially as an enzyme catalyst and antioxidant [8].

Antioxidants play an important role in minimizing cellular damage due to increased production of reactive oxygen and nitrogen species (eg, oxidative stress). Antioxidant defense systems include enzymes (e.g., superoxide dismutase, glutathione peroxidase), trace elements (e.g., selenium, zinc), vitamins (e.g., vitamins C, E, beta-carotene), sulfhydryl group donors (e.g., glutathione), and glutamine. Critical illness is associated with deficits in circulating antioxidants due to sepsis-induced redistribution from blood to tissues and decreased nutrient intake [29].

The resulting decrease in antioxidant potential increases cellular oxidative injury (particularly lipid peroxidation). A number of clinical studies have explored the potential benefits of supplementation with antioxidants. Combinations and doses of single antioxidants vary widely. Heyland *et al*. conducted a meta-analysis of clinical studies of trace elements and vitamin supplements in critically ill patients. They concluded that trace elements and vitamins that support antioxidant function, particularly high doses of selenium (either alone or in combination with other antioxidants), are safe and may be associated with reduced mortality. However, the optimal combination and dose of micronutrients remains to be determined [30].

4. Coconut fruit (*Cocus nucifera* L.)

Exploration of the potential wealth of crops in all respects one of which is coconut. The coconut, *Cocos nucifera* L., is a cultivated tree for its various uses, primarily for its nutritional and medicinal values. In addition, coconut is an environmentally friendly plant that allows coexistence with multi-species plants. This enriches soil fertility and is quite suitable for organic farming if the crop is grown in suitable inter-spaces. Due to its various uses in the present and the future, this plant has very bright potential.

The versatile coconut tree is a source of various chemical compounds that are responsible for various activities, especially activities for treatment or health. Recently, modern medicinal research has confirmed the many health benefits of various coconut products in various forms. Therefore, extensive investigations are needed to exploit its therapeutic uses for fighting disease. A drug development program must be carried out to develop modern drugs with their compounds isolated from coconut. Modern drugs need to be developed after extensive investigation of their bioactivity, mechanism of action, pharmacotherapy, after standardization and appropriate clinical trials. As the global scenario changes towards the use of non-toxic plant products used for traditional medicine, the development of modern

medicines from Cocus nucifera must be emphasized for the control of various diseases. Coconut that absorbs extraordinary potential needs special attention from its scientific fraternity to emerge as a milestone in the medical science history of this millennium because of its various medicinal uses. Further evaluation needs to be carried out on *C. nucifera* to explore hidden areas and their practical clinical applications, which can be used for the welfare of mankind.

Coconut (*Cocos nucifera* L.,) is a cultivated tree for its various uses, mainly for its nutritional and medicinal value. Various coconut products include young coconut water, copra, coconut oil, raw kernel, coconut cake, coconut shell, coconut shell and products made from wood, coconut leaves, coir pith and others. All parts of the coconut can be used in the daily life of people in traditional coconut growing areas. It is a unique source of various natural products for the development of medicines against various diseases and also for the development of industrial products. The fruit parts such as coconut hump and young coconut water have various medicinal properties such as antibacterial, antifungal, antiviral, antiparasitic, antidermatophyte, antioxidant, hypoglycemic, hepatoprotective, immunostimulant. Coconut water and coconut kernels contain microminerals and nutrients that are important for human health, therefore coconuts are used as food by people around the world, especially in tropical countries [31].

Coconut (*Cocos nucifera* L.) is a plant that is commonly found in tropical areas, especially Indonesia. Green coconut water, which is technically endosperm fluid, is formed in small amounts in the third month of seed development and reaches the highest amount in the eighth month and decreases after the seeds have matured [32].

Young coconut fruit is one of the unique tropical plant products because in addition to the flesh component that can be consumed directly, the fruit water component can also be drunk directly without going through processing. This uniqueness is supported by the physical properties and chemical composition of coconut meat and water, so that this product is very popular with consumers, both children and adults. In addition to having high economic value, young coconut fruit has a fairly good nutritional composition, including fatty acids and essential amino acids that are needed by the body. Meanwhile, coconut water, apart from being a fresh drink, also contains various minerals, vitamins and sugars as well as essential amino acids so that it can be categorized as a highly nutritious soft drink and can cure various diseases. However, for some consumers, consuming coconut water is only considered as a drink to relieve thirst. While the flesh is only as a complement after drinking the water. Compared to other soft drinks, coconut water which contains good nutrition can be categorized as a highly nutritious, hygienic and natural drink and has been proven to cure various diseases [33].

Coconut water contains macronutrients in the form of carbohydrates, fats and proteins as well as micronutrients in the form of vitamins and minerals. The vitamins contained in coconut water are vitamin B (B1, B2, B3, B5, B7, B9 and B12) and vitamin C and Nitrogen (N), Phosphorus (P), Potassium (K), Calcium (Ca) and Magnesium (Mg), whose levels decrease during maturity [34].

Coconut fruit (*Cocos nucifera* L.) contains high concentrations of polyphenols, and health-promoting phytonutrients. The content of components of phenolic compounds that are antioxidants (vitamin E from the monophenol group and phenolic acid from the polyphenol group) [35].

Young coconut flesh has a high nutritional composition, including fatty acids and essential amino acids that are needed by the body. While coconut water contains a variety of minerals, vitamins and sugars as well as essential amino acids, high nutritional value. Young coconuts contain amino acid components such as Glutamate (GLU) 14.50%; 4.02% of water and young coconut flesh, Arginine

(ARG) 12.75%; 2% of water and young coconut flesh, lauric acid 31.10% of young coconut flesh and vitamin C 2.2–3.4 mg/100 ml of young coconut water [33].

Barlina [36] has conducted research on the addition of young coconut meat (B1) 15%, (B2) 20% and (B3) 25% in the preparation of coconut drink powder. In addition, young coconut water is an endosperm fluid which is an excellent natural soft drink. It has a calorific value of 17.4/100 g. Coconut water contains B vitamins namely nicotinic acid B3 (0.64 g/mL), pantothenic acid B5 (0.52 g/mL), biotin (0.02 g/mL), riboflavin B2 (<0.01 g/mL).), folic acid (0.003 g/mL), trace amounts of thiamine B1 and pyridoxine B6 [37]. In addition, coconut water contains sugar, sugar alcohol, vitamin C, folic acid, free amino acids, phytohormones (auxin, 1, 3-diphenylurea, cytokinins), enzymes (acid phosphatase, catalase, dehydrogenase, diastase, peroxidase, RNA polymerase) and growth driving factor [38].

Coconut water, also known as coconut juice, is a natural refreshing drink common in the tropics [31, 39, 40], serving as a suspension of the coconut endosperm during the core phase of its development. Then, the endosperm matures and settles on the coconut shell during the cellular phase. Mature fruit has much less liquid than immature young coconuts. The health benefits of coconut water include: boosting the immune system, detoxifying and fighting viruses and helping cleanse the digestive tract [41]. The water from this coconut is a clear, colorless, sweet, natural drink that has a slightly sour taste. Decades of research has shown that coconut water is a rich source of nutrients, including essential amino acids (lysine, leucine, cystine, phenylalanine, tyrosine, histidine, and tryptophan), palmitic and oleic acids, vitamins and minerals [40–43]. Other minerals such as iron, zinc, copper and manganese are available at adequate levels [41, 44].

The free amino acid, L-arginine (30 mg/dL) is present in young coconut water which significantly reduces the formation of free radicals. Young coconut water also contains vitamin C (15 mg/100 mL) which significantly reduces lipid peroxidation when exposed to rats [45].

Young coconut water contains electrolytes that are very rich in inorganic ions such as K (290 mg%), Na (42 mg%), Ca (44 mg%), Mg (10 mg%), P (9.2 mg%) and others [46]. The concentration of these electrolytes in young coconut water produces an osmotic pressure similar to that observed in blood [9] and does not affect plasma coagulation. The high amount of K in coconut water has been reported to lower blood pressure [45]. The ethanolic extract of *C. nucifera* endocarp was found to have vasorelaxant and antihypertensive effects, via the production of nitric oxide in an endothelial-dependent concentration and manner, due to direct activation of the nitric oxide/guanylate cyclase pathway, stimulation of muscarinic receptors and/or via the cyclooxygenase pathway [47].

Young coconut water has many medicinal properties, according to Effiong *et al* [47], including a good drink for cholera patients because of its salt and albumen content; check for urinary tract infections, and diarrhea. The most abundant and powerful medium-chain saturated fatty acid (MCFA) in coconut is lauric acid, which accounts for nearly 50% of coconut fat content. MCFA and its derivatives such as monoglycerides (MG) found in coconut are effective in destroying a wide variety of lipid-coated bacteria by destroying their lipid membranes. For example, it is effective against bacteria that can cause heartburn, sinusitis, cavities, food poisoning, and urinary tract infections. Monoglycerides, particularly Monolaurin, have been used to protect the composition of intravenously adjustable oil-in-water emulsions against the growth of Escherechia coli (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*) and *Candida albicans* (*C. aeruginosa*). albicans). The 1.25 mM monolaurin emulsion in citrate-lactate buffer at pH 4 to 5 resulted in a > 6 to 7-log10 reduction in the number of Salmonella spp. and *E. coli* within 10 minutes [48]. Lauric acid, which is also present in breast milk,

helps protect nursing infants from harmful pathogens [49], as contained in many other important medicinal plants which have antibacterial properties [50, 51]. *C. nucifera* is also very good against different pathogenic bacteria that cause several life-threatening infections in humans [52].

5. Kaffir lime fruit (Citrus Hystric DC.)

Antioxidant production is a control mechanism of the tissue to balance the concentration of ROS. Endogenous antioxidants such as glutathione, pyruvate, and lycopene are produced by the body to deal with the effects of oxidative stress. If the concentration of endogenous antioxidants is insufficient or unbalanced, exogenous antioxidants need the help of exogenous antioxidants. Exogenous antioxidants can be obtained from various sources such as synthetic antioxidants (vitamin E and Vitamin C) and natural antioxidants derived from plants [53].

Kaffir lime (*Citrus hystrix*) is a plant that grows in Indonesia, Malaysia, and Thailand. Citronelal, a monoterpenoid compound that has strong antioxidant activity so that it can be used as an alternative to exogenous antioxidants [54].

Kaffir lime is a fruit that is known to the public as a food source and used as herbal medicine with very high antioxidant activity, so it is widely used in daily needs [55]. Plants of the Citrus genus are known to be rich in polyphenols [56], considered to be one of the antioxidant resources containing sufficient amounts of ascorbic acid/vitamin C, tocopherols, flavonoids, –carotene and other phenolic compounds [57–60]. Polyphenols and flavonoids are good electron donors with their antioxidant power varies from one compound to another [61, 62].

6. Nutrition related to immune function

Along with the development of science and technology, nutrients that are known to have immunomodulating effects are prebiotics, proteins/amino acids, fats/fatty acids, vitamins and minerals.

6.1 Protein amino acids related to immune function contained in coconut fruit for the treatment of infectious diseases and sepsis

The protein contained in the flesh of young coconuts contains 15 types of amino acids, 10 of which include essential amino acids. The ten essential amino acids are threonine (THR), tyrosine (TYR), methionine (MET), valine (VAL), phenylalamine (PHE), ileucine (ILE), leucine (LEU), lysine (LYS), histidine (HIS). and arginine (ARG). HIS and ARG are not essential for adults, but essential for children. In addition, the amino acid content of Glutamate (GLU) in all types of coconut ranged from 3.59–4.02%, which was the highest compared to other types of amino acids. Thus, consuming young coconut flesh in addition to being able to fulfill some of the essential amino acid needs while at the same time obtaining GLU amino acids where these amino acids are important nutrients in infectious conditions [33].

Glutamine (GLU) has many roles in the immune system. Glutamine supplementation has been reported to have multiple benefits, including increasing nitrogen retention and reducing muscle cell mass loss, enhancing immune function, thereby reducing the risk of infection and maintaining organ glutamine. Glutamine is an essential nutrient for enterocytes and immune cells through its antioxidant and cytoprotective effects. Glutamine maintains the protective function of the gut, provides antioxidant and cytoprotective effects, stimulates nucleotide synthesis,

maintains the killing of neutrophil bacteria, and increases the proliferation and secretion of lymphocytes and macrophages. Intense immune activity and/or hypercatabolism, as occurs in burns, trauma and sepsis, is associated with increased glutamine consumption and a drastic decrease in plasma glutamine concentrations. Loss of glutamine concentration during the body's defense processes can lead to severe impairment of immune function. Hypoglutaminemia is an independent predictor of mortality and/or poor clinical outcome in critically ill patients [63, 64].

Glutamine is the most common free amino acid in the body with various involvements in gluconeogenesis, ammoniagenesis in the kidney, and the integrity of the intestinal mucosa. Glutamine is also conditionally important during catabolic conditions as it provides oxidative energy for cell division, increases antioxidant production, and acts as a major fuel for intestinal cells and the immune system [17, 65].

Glutamine supplementation has been shown to have multiple benefits, including increasing nitrogen retention and reducing muscle mass loss, maintaining the permeability and structure of the gastrointestinal mucosa, enhancing immune function thereby reducing the risk of infection and maintaining organ glutamine [66, 67].

Sepsis is accompanied by increased consumption, impaired synthesis, and decreased supply of the semi-essential amino acid arginine. This state of arginine deficiency impairs immune homeostasis and increases the risk of nosocomial infections. L-arginine supplementation is thought to contribute to restoring physiological processes such as its role for protein synthesis, organ perfusion, and wound healing in septic patients [68].

Meanwhile, arginine is an essential amino acid which during pathophysiological stress such as sepsis and trauma, its synthesis decreases. The immunomodulatory effect of arginine lies in increasing the function of B and T lymphocytes and their macrophages. Arginine is also involved in many anabolic processes involved in wound growth and healing, as it participates in connective tissue synthesis, changes in blood flow, and angiogenesis [16, 65].

Arginine can stimulate the release of growth hormone, prolactin, and insulin, as well as increase the number of T cells and improve T cell function. During catabolic disease serum arginine levels decrease due to reduced food intake, increased uptake in the endothelium, liver, and intestines and increased metabolism [69]. In addition, increased arginase expression leads to arginine depletion and decreased T cell activation and immunocompetence, and an increased risk of infection. So it is hypothesized that arginine supplementation can inhibit arginase and prevent these negative symptoms [70].

6.2 Fatty acids related to immune function contained in coconut fruit for the treatment of infectious diseases and sepsis

Clinical trials have shown that unsaturated fatty acids can be considered as powerful disease-modifying nutrients in patients with acute lung injury and sepsis [71, 72]. In particular, feeding with polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA), and docasahexaenoic acid (DHA) has been found to attenuate the production of various cytokines, chemokines, and other effectors [73]. Moreover, the recent discovery of resolvin produced by EPA and DHA has shed more light on the resolution of inflammation, as a possible mechanism of the anti-inflammatory action of the 3 PUFAs during systemic inflammation [74].

To determine the fat quality of young coconut flesh, Rindengan *et al*. [75] have analyzed the fatty acid and amino acid composition of young coconut flesh. In addition, young coconut flesh contains carbohydrates, crude fiber, galactomannan, phospholipids and a number of macro and micro minerals. Coconut fruit contains unsaturated fatty acids (ALT) oleic or omega 9 and essential ALTJ linoleic or omega

6. In general, products on the market such as formula milk include the weight of the two types of fatty acids. Omega 9 and omega 6 fatty acids occur naturally in several types of plant foods [75]. Omega 6 is one type of essential fatty acid that must be obtained from food because it cannot be metabolized in the body. In the body, omega 6 will be metabolized into arachidonic acid (AA). AA and linoleic (omega 6) ranks 2nd and 3rd of the four types of fatty acids that support brain intelligence. Docosahexanoic acid (Docosahexaenoic acid, DHA) is in first place and linolenic acid (omega 3) is fourth. Linolenic acid is an essential that must be obtained from food and in the body will be metabolized into DHA [76].

Given the high content of omega 9 and omega 6 fatty acids in young coconut meat, young coconuts can be an alternative to meet the needs of these two types of fatty acids. Seeing the nutritional potential that is also contained in the flesh of young coconuts, it is better not only to consume coconut water but together with coconut meat. Omega 6 essential unsaturated fatty acids (ALTJ) (linoleic) are classified as double ALTJ (Polyunsaturated fatty acids, PUFAs) [33].

6.3 Vitamins, Carotenoids and Flavonoids related to immune function contained in coconuts for the treatment of infectious diseases and sepsis

6.3.1 Vitamin B

Vitamin B12, vitamin B6, folic acid and niacin are B vitamins that are beneficial for the immune system. Vitamin B6 contributes in the proliferation of lymphocytes, the formation of lymphoid tissue and in the antibody response. Vitamin B12 plays a role in augmenting the performance of phagocytes and T cell proliferation. Folic acid together with vitamin B12 can affect Natural Killer cells [24, 77, 78].

6.3.2 Vitamin C

Vitamin C is an enzyme catalyst and antioxidant. In addition, vitamin C is a regulator of immune cell activation to maintain the viability of immune cells. Vitamin C functions in the synthesis of nitric oxide produced by macrophages, regulates phagocytosis by reducing free radical production and increasing the activity of immune cells (natural killer) [79].

Vitamin C has important vascular protective effects by inhibiting oxidative stress, modulating intracellular signaling pathways, and maintaining homeostatic nitricoxide levels [80]. Vitamin C is also an important cofactor for the production of endogenous norepinephrine, epinephrine, and vasopressin [81]. Septic patients usually have very low or undetectable serum vitamin C levels [82].

Vitamin C can reduce the expression of iNOS ascorbate and can overcome radicals produced by the immune system. Ascorbate also reduces or prevents endotoxin translocation from the gut and is directly bactericidal, and can increase circulating GSH concentrations in the liver. Ascorbate also prevents the reduction of enzymes in the liver and is responsible for endotoxin clearance [26]. In a study conducted by Crimi *et al*., administration of high doses of vitamin C and vitamin E can reduce mortality by 67.5% to 45.7% [83].

6.3.3 Vitamin E

Vitamin E (tocotrienol or -tocopherol) is a powerful antioxidant that can assist monocyte/macrophage-mediated immune responses and IL-2 [79]. Vitamin E and other antioxidants increase CD4 cells. Vitamin E inhibits the synthesis of prostaglandins produced in cells after membrane oxidation, prevents fatty acid peroxidation

and is an immunoregulator of arachidonic acid metabolism through the synthesis of prostaglandins and leukotrienes. Vitamin E also affects T cells, B cells and monocytes and regulates the response of the cyclic element AMP that binds to protein [84].

6.3.4 Carotenoids and flavonoids

Supplementation of carotenoids and flavonoids causes an immunostimulator effect in the form of an increase in Th cells and NK cells, IL-2 receptors. Research has shown the ability of carotenoids to influence the production of cytokines, namely TNF alpha and IL-1, and T cell proliferation, as well as flavonoids to influence inflammation, cytokine production, lymphocyte and granuloside production through mechanisms of protection against free radicals, regulation of NO and arachidonic acid metabolism [85].

6.4 Minerals related to immune function contained in coconut fruit for the treatment of infectious diseases and sepsis

6.4.1 Zinc (Zn)

Zinc is an important component in the regulation of gene expression through its role in gene transcription, division, differentiation, and cell apoptosis [86]. Zinc in the immune system plays a role in mechanical barriers (the structure and function of the gastrointestinal epithelium), as an antioxidant, in thymid kinase activity (plays a role in the proliferation of lymphoid cells), thiomulin and increases IgAs [87, 88].

Zinc is a co-factor of more than 200 enzymes that play a role in the immune system. It is very important for the wound healing process, regenerate new cells and balance acid base. Zinc has a very important role for the immune system, oxidative stress response, wound healing process and protective homeostasis. Symptoms of zinc deficiency and sepsis are difficult to distinguish. Several enzymes that play a role in regulating oxidant defense, including SOD, catalase, and glutathione reductase, depend on normal zinc conditions. It is suitable because in sepsis there is a decrease in the detoxification capacity of ROS [88].

6.4.2 Selenium (Se)

Selenium is a component of selenoproteins with antioxidant, anti-inflammatory and immunomodulatory properties. Low selenium concentrations in patients with systemic inflammation or sepsis are associated with impaired neutrophil and macrophage function and decreased antioxidant defenses. The effect of selenium treatment may depend on dose, route of administration, combination with other nutrients, and the patient population studied [89].

Selenium has an antioxidant function through the activity of the enzyme glutathione peroxidase which protects cell membranes and organelles from peroxide damage and has a synergistic effect with vitamins C and E. In addition, selenoproteins (selenium derivatives) are components of the body's defenses that affect the function of neutrophils, macrophages, NK cells and lymphocytes T [79].

6.4.3 Copper (Cu)

Sepsis is often accompanied by acidosis and the release of cupric ions from ceruloplasmin and other proteins. With increased oxygen demand that is not accompanied by oxygen availability causes ischemia and acidosis in early sepsis and the release of cupric ions [90].

Copper is an essential trace mineral necessary for survival. It is found in all body tissues and plays a role in making red blood cells and maintaining nerve cells and the immune system. Copper may also have an antioxidant function. It may help reduce the production of free radicals [91].

Copper is an important component of several enzymes such as superoxide dismutase (SOD), cytochrome oxidase and several coenzymes. Necessary for hemoglobin formation, antioxidant effect, immune function and collagen synthesis. Copper consumption is limited for patients with liver failure and cholestasis because it is excreted through the gallbladder and will cause poisoning if it accumulates [92].

6.4.4 Iron (Fe)

Iron affects the function of lymphocytes and macrophages, which is related to its role as a cofactor for enzymes in various processes. Lymphocyte activation requires iron because iron plays an important role in the work of several enzymes including nucleotide reductase which is involved in DNA synthesis. Iron uptake is regulated by transferrin mRNA receptors by binding to iron regulatory proteins (IRPs). In the state of iron deficiency, transferrin only binds a small amount of iron which will interfere with proliferation, on the contrary, in iron overload, transferrin saturation will increase and will inhibit lymphocyte proliferation [93].

In sepsis, the decrease in iron concentration occurs because of increased permeability so that transferrin moves from the intravascular to the interstitial fluid. The increase in ferritin production in the liver is caused by the induction of IL-6 so that more Fe is stored in the liver. In sepsis, hepcidin production is increased and will inhibit Fe transport [94]. Neutrophils and macrophages require Fe for phagocytosis and the formation of oxygen intermediates which are toxic in killing bacteria. The reduction of nitroblue tetrazolium and hydrogen peroxide to neutrophils and macrophages is decreased in the presence of iron deficiency. Iron also plays a role in the Crebs cycle as an essential source of energy. Several enzymes such as glutathione, peroxidase, catalase and dehydrogenase require iron as a free radical scavenger [95, 96]. Increased venous permeability causes leakage of transferrin into the interstitial fluid. Iron stimulates bacterial growth because of its role as an essential nutrient for bacterial growth [94]. Polymorphonuclear (PMN) releases lactoferrin through the inflammatory process and bends iron which is then processed by macrophages. Neutrophils and macrophages need iron for phagocytosis and killing bacteria. Otherwise, excessive iron can decrease the ability of macrophages to carry out phagocytosis. This happens because the production of free radicals is increasing and damaging the lipid peroxidase contained in the phagosome membrane. Iron is also a growth factor for some bacteria and promotes overall proliferation in vivo [96].

7. Conclusions

An immunonutrient test preparation containing 20% young coconut flesh in coconut water and added kaffir lime juice has a very strong antioxidant activity influenced by the components found in coconut fruit (*Cocos nucifera* L.,) namely a component of a mixture of phytonutrients that can be used as immunonutrient agents in sepsis caused by Lipopolysaccaride *Escherichia coli* through antioxidant activity. The addition of kaffir lime juice can inhibit rancidity or rancidity arising from the oxidation of unsaturated fatty acids contained in processed coconut meat so as to maintain the stability of the components of the active compounds contained in processed coconuts so that these preparations can provide good treatment results.

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References

[1] Joshi RK. Role of natural products against microorganisms. Am J Clin Microbiol Antimicrob. 2018;1:1-5.

[2] Southwick F S. Infectious diseases: A clinical short course. Mc Graw Hill; 2007. 57- 65 p.

[3] Kang-Birken, S. Lena. Sepsis and Septic Shock. In: Dipiro, J.T., Talbert R.L., Yee, G.C., Matzke, G.R., Wells, B.G., and Posey, L.M., Pharmacotherapy A Pathophysiology Approach Ninth Edition. United States of America: The McGraw-Hill Companies Inc.; 2014. 1897-1910p.

[4] Gantner, D., Mason, C. Management of severe sepsis. Anaesth. Intensive Care Med. 2015;16:593-597. https://doi.org/10.1016/j.mpaic.2015.09.012

[5] Guntur A.H. Sepsis: SIRS, Sepsis, dan Syok Sepsis (Imunologi, Diagnosis, Penatalaksanaan). Surakarta: Sebelas Maret University Press; 2008. 1-8 p.

[6] S.B. Levy, B. Marshall. Antibacterial resistance worldwide: Causes, challenges and responses. Nat. Med. 2004;10: 122-129, https://doi.org/10.1038/nm1145.

[7] Garrido A.G, Poli de Figueiredo L.F, Rocha e Silva M. experimental models of sepsis and septic shock : An overview. Acta Cirurgica Brasileira. 2004;19(2):82-88.

[8] De Waele E, Malbrain MLNG, Spapen H. Nutrition in sepsis: A bench-tobedside review. Nutrients. 2020;12:1-16.

[9] Paul Wischmeyer, M.D. Nutrition therapy In sepsis. Crit Care Clin. 2018; 34(1):107-125.

[10] Hotchkiss, R.S.; Monneret, G.; Payen, D. Sepsis-induced immunosuppression: From cellular dysfunctions to immunotherapy. Nat. Rev. Immunol. 2013;13:862-874. https://doi.org/10.103

[11] Tom van der Poll, Frank L. van de Veerdonk, Brendon P. Scicluna & Mihai G. Netea. The immunopathology of sepsis and potential therapeutic targets. Nature Reviews Immunology. 2017;17:407-420.

[12] Cecconi, M.; Evans, L.; Levy, M.; Rhodes, A. Sepsis and septic shock. Lancet. 2018;392:75-87.

[13] Akram M. Salam and Cassandra L. Quave. Opportunities for plant natural products in infection control. Curr Opin Microbiol. 2018;45:189-194. doi: 10.1016/j.mib.2018.08.004.

[14] Vetvicka, V, Vetvickova, J. Concept of Immuno-Nutrition. Journal of Nutrition & Food Sciences. 2016; 6(3).

[15] Grimble, R. F. Basics in clinical nutrition: Immunonutrition – Nutrients which influence immunity: Effect and mechanism of action. E-SPEN. The European E-Journal of Clinical Nutrition and Metabolism. 2008;4(1):10-13. doi:10.1016/j.eclnm.2008.07.015

[16] Roehl, K. Immunonutrition in 2016: Benefit, harm or neither? Practical Gastroenterology. 2016; 154: 27-40.

[17] Calder, P. C. Immunonutrition may have beneficial effects in surgical patients. The BMJ, 2003;327(117): 117-118.

[18] Grimble, R. F. Basics in clinical nutrition: Immunonutrition – Nutrients which influence immunity: Effect and mechanism of action. E-SPEN. The European E-Journal of Clinical Nutrition and Metabolism, 2008;4(1):10-13. doi:10.1016/j.eclnm.2008.07.015

[19] Pierre JF, Heneghan AF, Lawson CM, Wischmeyer PE, Kozar RA, Kudsk KA. Pharmaconutrition review: Physiological mechanisms. J Parenter Enter Nutr. 2013;37:51-65.

[20] McCarthy MS, Martindale RG. Immunonutrition in critical illness: What is the role? Nutr Clin Pract. 2018;33(3):348-358.

[21] Zong J, Martirosyan DM. Anticancer effects of garlic and garlic-derived bioactive compounds and its potential status as functional food. Bioactive Compounds in Health and Disease. 2018;1(2):16-35.

[22] Osland E, Memon B, Memon MA. Pharmaconutrition administration on outcomes of elective oncological surgery for gastrointestinal malignancies: Is timing everything? — A review of published meta-analyses until the end of 2016. Translational Gastroenterology and Hepatology. 2018;3(52):1-8.

[23] McCarthy MS, Martindale RG. Immunonutrition in critical illness: What is the role? Nutr Clin Pract. 2018;33(3):348-358.

[24] Mizock BA, Sriram K. Perioperative immunonutrition. Expert Rev Clin Immunol. 2011;7(1):1-3.

[25] Agung Prasetiyo, Nasronudin. Micronutrient therapy for sepsis. Indonesian Journal of Tropical and Infectious Disease. 2015;5(5):119-123.

[26] Shenkin A. The key role of micronutrients. Clinical Nutrition. 2005;25:1-13.

[27] Rahmayati Rusnedy. Uji antioksidan campuran buah kelapa muda dan air perasan jeruk purut sebagai imunonutrisi pada tikus terinduksi sepsis. Riset Informasi Kesehatan. 2020;9(2):37-45.

[28] Putra AP. Pengaruh penambahan minyak jeruk purut terhadap proses penghambatan ransiditas pada minyak kelapa. Universitas Brawijaya; 2016.

[29] Berger MM, Chiolero RL. Antioxidant supplementation in sepsis and systemic inflammatory response syndrome. Crit Care Med. 2007;35:584-590.

[30] Heyland DK, Dhaliwal R, Suchner U, Berger M. Antioxidant nutrients: A systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med. 2005;31:327-337.

[31] M. DebMandal and S. Mandal, Coconut (Cocos nucifera L.: Arecaceae): In health promotion and disease prevention. Asian Pacific Journal of Tropical Medicine. 2011;1:241-247. doi:10.1016/S1995-7645(11)60078-3.

[32] Duarte, A.C.P., Coelho, M.A.Z., Leite, S.G.F. Identification of peroxidase and Tyrosinase in green coconut water. Cienc. Tecnol. Aliment. 2002;3(5):266-270.

[33] Barlina R,. Potensi Buah Kelapa Muda Untuk Kesehatan dan Pengolahannya. Perspektif. 2004;3(2):46-60.

[34] Farapti dan Savitri Sayogo. Air Kelapa Muda–Pengaruhnya terhadap Tekanan Darah. Jurnal CDK-23. 2014;41(12):896-900.

[35] Pulung ML, Yogaswara R. Oil Dari Tanaman Kelapa Asal Papua. Chem Prog. 2016;9(2):63-69.

[36] Barlina R. Pengaruh Perbandingan Air Kelapa Dengan Penambahan Daging Kelapa Muda. J Littri. 2007;13(2):73– 82.

[37] United States Department of Agriculture (USDA). National nutrient database for standard reference, Nuts, coconut water, 2008. [Online]. Available

from: http://www.nal.usda.gov/fnic/ foodcomp/ cgi-bin/list_nut_edit.pl/. [Accessed on December 8, 2009].

[38] Yong WJWH, Ge L, Ng YF, Tan SN. The chemical composition and biological properties of coconut (Cocos nucifera L.). Molecules. 2009;14:5144-5164.

[39] A. M. Fonseca, F. J. Q Monte, M. da Conceic and F. de Oliveiraa ão. Coconut Water (*Cocos nucifera* L.)—A New Biocatalyst System for Organic Synthesis. Journal of Molecular Catalysis B: Enzymatic. 2009;57:78-82. doi:10.1016/j.molcatb.2008.06.022

[40] E. H. M. Walter, D. Y. Kabuki, L. M. R. Esper, A. S. Sant'Ana and A. Y. Kuaye. Modelling the growth of listeria monocytogenes in fresh green coconut (Cocos nucifera L.) water. Food Microbiology. 2009;26:653-657. doi:10.1016/j.fm.2009.04.003

[41] Campbell-Falck D. Thomas T. Falck TM. Tutuo N. Clem K. The intravenous use of coconut water. American Journal of Emergency Medicine. 2000;18(1):108-111.

[42] U. Santoso, K. Kubo, T. Ota, T. Tadokoro and A. Maekawa. Nutrient composition of Kopyor coconuts (Cocos nucifera L.). Food Chemistry. 1996;57(2):299-304. doi:10.1016/0308-8146(95)00237-5

[43] A. G. Pue, W. Riva, K. Sundarao, C. Kaluarin and K. Singh. Preliminary studies on changes in the coconut water during maturation of the fruit. Science in New Guinea. 1992;18(2):81-84.

[44] A. Jayalakshmy, C. Arumughan, C. S. Narayanan and A. G. Mathew. Changes in the chemical composition of coconut water during maturation. Journal of Food Science and Technology. 1986;23(4):203-207.

[45] Loki AL, Rajamohan T. Hepatoprotective and antioxidant effect of tender coconut water on CCl4 induced liver injury in rats. Indian J Biochem Biophy 2003;40(5):354-357.

[46] Effiong GS, Ebong PE, Eyong EU, Uwah AJ, Ekong UE. Amelioration of chloramphenicol induced toxicity in rats by coconut water. J Appl Sc Res. 2010; 6(4):331-335.

[47] Bankar GR, Nayak PG, Bansal P, Paul P, Pai KSR, Singla RK, et al. Vasorelaxant and antihypertensive effect of Cocos nucifera Linn. Endocarp on isolated rat thoracic aorta and DOCA saltinduced hypertensive rats. J Ethnopharmacol. 2010;134(1):50-54. doi:10.1016/ j.jep.2010.11.047

[48] Thormar H, Hilmarsson H, Bergsson G. Stable concentrated emulsions of the 1-monoglyceride of capric acid (monocaprin) with microbicidal activities against the food-borne bacteria campylobacter jejuni, salmonella spp., and Escherichia coli. Appl Environ Microbiol. 2006;72(1):522-526.

[49] Thormar H, Hilmarsson H. The role of microbicidal lipids in host defense against pathogens and their potential as therapeutic agents. Chem Phy lipids. 2007;150(1):1-11.

[50] Mandal S, Mandal MD, Pal NK, Saha K. Synergistic antiStaphylococcus aureus activity of amoxicillin in combination with Emblica officinalis and Nymphae odorata extracts. Asian Pacific J Trop Med. 2010;3:711-714.

[51] Mandal S, Mandal M, Pal NK. Antibacterial potential of Azadirachta indica seed and Bacopa monniera leaf extracts against multidrug resistant salmonella enterica serovar Typhi isolates. Archives Med Sci. 2007;3:14-18.

[52] Obi RC, Oyi AR, Onaolapo JA. Formulation and antimicrobial activities of coconut (Cocos nucifera Linne) oil. Research Journal of Applied Sciences,

Engineering and Technology. 2010;2(2):133-137.

[53] Pouillot A, Luigi LP, Philippe T, Alice N, Ada P and Barbara P. Formulating, Packaging, and Marketing of Natural Cosmetic Products. New York: Wiley; 2011.

[54] Mahalwal VS and AliM.Volatile Constituents of the Fruit Peels of C. reticulate. Blanco J Essent Oil Bearing Plants. 2001;4:45-49.

[55] Rahmi U, Manjang Y, Santoni A. Profil Fitokimia Metabolit Sekunder Dan Uji Aktivitas Antioksidan Tanaman Jeruk Purut (Citrus histrix DC) dan jeruk bali (Citrus maxima (Burm.f.) Merr). J Kim Unand. 2013;2(2):109-114.

[56] Swallah MS, Sun H, Affoh R, Fu H, Yu H. Antioxidant Potential Overviews of Secondary Metabolites (Polyphenols) in Fruits. Int J Food Sci. 2020. doi. org/10.1155/2020/9081686

[57] Al-Juhaimi FY, Ghafoor K. Bioactive compounds, antioxidant and physicochemical properties of juice from lemon, mandarin and orange fruits cultivated in Saudi Arabia. Pakistan J Bot. 2013;45(4):1193-1196.

[58] Ching LS, Mohamed S. AlphaTocopherol content in 62 edible tropical plants. J Agric Food Chem. 2001;49(6):3101–3105.

[59] Ghasemi K, Ghasemi Y, Ebrahimzadeh MA. Antioxidant activity, phenol and flavonoid contents of 13 citrus species peels and tissues. Pak J Pharm Sci. 2009;22(3):277-281.

[60] Siripongvutikorn, S., P. Thummaratwasik and Y. Huang. Antimicrobial and antioxidation effects of Thai seasoning, Tom-Yum. Lebensm. Wiss. U. Technol. 2005;38:347-352.

[61] Bourgou S, Ksouri R, Bellila A, Skandrani I, Falleh H, Marzouk B. Phenolic composition and biological activities of Tunisian Nigella sativa L. shoots and roots. Comptes Rendus - Biol. 2008;331(1):48-55.

[62] Naczk M, Shahidi F. Extraction and analysis of phenolics in food. J Chromatogr A. 2004;1054(1-2):95-111.

[63] Wischmeyer P.E. Glutamine: Mode of action in critical illness. Crit. CareMed. 2007;35:541-544.

[64] Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: Metabolism and immune function, Supplementation and Clinical Translation. Nutrients. 2018;10(11):1564.

[65] Calder, P: Overview of nutrients with their functions and effects. The BMJ. 2003;327(7407):117-118.

[66] Bengmark S. Modulation by enteral nutrition of the acute phase response and immune functions. Nutr Hosp. 2003;18(1):1-5.

[67] Novak F, Heyland D, Avenell A, Drover J, Su X. Glutamine Supplementation in Serious Illness ; A Sytematic Review of the Evidence. Crit Care Med. 2002;30(9):2022-2029.

[68] Davis, J.S.; Anstey, N.M. Is plasma arginine concentration decreased in patients with sepsis? A systematic review and meta-analysis*. Crit. Care Med. 2011;39:380-385.

[69] Waitzberg DL, Saito H, Plank LD, et al. Postsurgical infections are reduced with specialized nutrition support. World J Surg. 2006;30:1592-1604.

[70] Pan M, Choudry HA, Epler MJ, et al. Arginine transport in catabolic disease states. J Nutr. 2004;134(10):2826-2829.

[71] Singer P, Theilla M, Fisher H, et al. Benefit of an enteral diet enriched with

eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med. 2006;34(4):1033-1038.

[72] Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med. 2006;34(9):2325-2333.

[73] Singer P, Shapiro H, Theilla M, et al. Anti-inflammatory properties of omega-3 fatty acids in critical illness: Novel mechanisms and an integrative perspective. Intensive Care Med. 2008;34(9):1580-1592.

[74] Serhan CN, Savill J. Resolution of inflammation: The beginning programs the end. Nat Immunol. 2005;6(12):1191-1197.

[75] Rindengan, B., A. Lay., H. Novarianto., H. Kembuan dan Z. Mahmud. Karakterisasi daging buah Kelapa Hirbida untuk bahan baku industri makanan. Laporan Hasil Penelitian. Kerjasama Proyek Pembinaan Kelembagaan Penelitian Pertanian Nasional, Badan Litbang; 1995;49.

[76] Clandinin and Jumpsen. Brain development: Relationship to Dietary lipid and Lipid Metabolism. AOCS Press: Champaign. Illinois; 1995.

[77] Heys S, Schofield A, Wahle W. Immunonutrition in clinical practice : What is the current evidence? Nutr Hosp. 2004;14(6):325-332.

[78] Duggan C, Gannon J, Walker WA. Protective nutrients and functional foods for the gastrointestinal tract. Am J Clin Nutr. 2002;75(5):789-808.

[79] Cunningham-Rundles S, Moon A, McNeeley DF. Malnutrition and host defense. Dalam: Duggan C, Watkins JB, Walker WA, penyunting. Nutrition in pediatrics. Edisi. Ontario: BC Decker Inc; 2008.261-271p.

[80] Wilson, J.X.; Wu, F. Vitamin C in Sepsis. Sub-cell. Biochem. 2012;56:67-83.

[81] May, J.M.; Harrison, F.E. Role of vitamin C in the function of the vascular endothelium. Antioxid. Redox Sign. 2013;19(17):2068-2083.

[82] Carr A.C, Rosengrave P.C, Bayer S, Chambers S, Mehrtens J, Shaw G.M. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care. 2017;21(1):300.

[83] Kalokerinos A, Dettman I, Meakin C. Endotoxin and vitamin C part 1 – Sepsis, endotoxin and vitamin C. J. Aust. Coll. Nutr. & Env. Med, 2005;24(1):17-21.

[84] Fernandes G, Jolly CA, Lawrence RA. Nutrition and the immune system. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, penyunting. Modern Nutrition In Health And Disease, 10 Edition Baltimore: Lippincot Williams; 2006.

[85] Gershwin ME, German JB, Keen CL. Nutrition and Immunology Principles and Practice: Human Press; 2000.

[86] Savino W, Dardenne M, Velloso LA, Silva-Barbosa SD. The thymus is a common target in malnutrition and infection. Br J Nutr. 2007;98(1):11-16.

[87] Bhaskaram P. Micronutrient malnutrition, infection and immunity: An overview. Nutr Rev. 2002;60(5):40-45.

[88] Cunningham-Rundles S, Moon A, McNeeley DF. Malnutrition and host defense. In: Duggan C, Watkins JB, Walker WA, penyunting. Nutrition in

pediatrics. Edisi. Ontario: BC Decker Inc; 2008. 261-271p.

[89] Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. Crit. Care Med. 1998;26(9):1536-1544.

[90] Roberts A, Bar-Oy D, Winkler J, Rael L. Copper-induced oxidation of epinephrine: Protective effect of D-DHAK, a synthetic analogue of the high affinity copper binding site of human albumin. Biochemichal and Biophysical Research Communication. 2003;304:755-757.

[91] Megan Ware, RDN, L.D. Free Radicals Can Damage Cells and DNA, Leading to cancer and Other Diseases; 2017.

[92] Braunschweig C, Sowers M, Kovacevich D. Parenteral zinc supplementation in adult humans during the acute phase response increases the febrile response. The Journal of Nutrition. 1997;127(1):70-74.

[93] Brock J, Mulero V. Cellular and molecular aspects of iron and immune function. Proceedings of Nutrition Society. 2000;59(4):537-540.

[94] Shenkin A. The key role of micronutrients. Clinical Nutrition. 2006;25(1):1-13.

[95] Agarwal A, Khana P, Baidya D, Arora met. Trace elements in Criticall illness. Journal of Endocrinology and Metabolism. 2011;2(1):57-63.

[96] Doherty P, Weaver L, Prentice A. Micronutrient supplementation and infection: A double-edge sword?. Journal of Pediatric Gastroenterology and Nutrition. 2002;34(4):346-352.