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Molecular and Immunological Mechanisms of Miana Leaf (*Coleus Scutellariodes* [L] Benth) in Infectious Diseases

Theo Audi Yanto[1], Mochammad Hatta[2], Agussalim Bukhari[3] and Rosdiana Natzir[4]

[1]Department of Internal Medicine Faculty Medicine Universitas Pelita Harapan, Tangerang, Indonesia.
[2]Department of Molecular Biology and Immunology, Faculty Medicine, Hasanuddin University, Makassar, Indonesia.
[3]Department of Nutrition, Faculty Medicine Universitas Hasanuddin, Makassar, Indonesia.
[4]Department of Biochistry, Faculty Medicine Universitas Hasanuddin, Makassar, Indonesia.
*Corresponding Author E-mail: hattaram@yahoo.com

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Infectious disease is still a massive world burden of disease. It causes premature mortality and morbidity. Regardless of antibiotic therapy, the increased numbers of antibiotic resistance bring emerging problems in infectious disease. Several pathogens have unique roles to deactivate host immune response causing difficulty to treat the infection. Alack of antibiotic efficacy is crucial to modulate the immune response as a brilliant strategy to face infectious disease in years to come. Various herbal medicine has been known to have a total role in enhancing immune response at the molecular level. Miana leaves extract (MLE) has a potential role in regulating the immune response to the infection. Besides its antimicrobial effect, MLE has other properties such as anti-inflammation, antioxidant. Several studies have revealed the molecular mechanism of MLE in immune response, such as enhancing IL 37, IL 10, regulating TLR 4, and IFN-g. The objectives of this article are to review the molecular and immunological mechanism of Miana in treating various infective diseases comprehensively.

Keywords: Coleus, infectious disease, immunology, miana, molecular.

Infectious diseases, caused by microorganisms such as bacteria, viruses, fungi, and parasites, are associated with a significant amount of worldwide morbidity and mortality. In 2008, the *World Health Organization* (WHO) stated that 1 billion population suffered from one or more infectious diseases per year.[1] Substantial year-to-year variation emphasizes the dynamic nature of infectious diseases.[2]

There was a 47% decrease in premature mortality and disability caused by infectious disease from 1990 to 2017. It correlates with better sanitation management, healthcare system, and antibiotics resistance.[3]However, irrational antibiotic prescribing leads to antimicrobial resistance (AMR).[4]The AMR bacteria cause healthcare-associated as well as community-acquired infections resulted from urinary tract infections or pneumonia.[5]

Furthermore, the development of novel antibiotics remains insufficient to handle the increasing AMR. Since the 1st of July 2017, eight new antibacterial agents have been approved, but their efficacy has been limited.[4]Therefore,

adjuvant therapies are being proposed as an option in managing infectious diseases.[67]Herbal medicine has known that has the potential to enhance the effect of standard treatment in many diseases from degenerative diseases to infectious diseases.[8910]Each of them has a unique collaborative pathway in treating the ailment. Nevertheless, herbal medicine which has potential benefit as an adjuvant still needs to evaluate its efficacy and biomolecular mechanism.[111213]

Furthermore, several plants and other natural resources have been used as herbal medicine such as purple miana leaves[14], curcumin[15], Moringa leaf extract[16], Sapodilla fruit extract[17], Curcuma longa extract[1819], Andaliman fruit extract (*Zanthoxylum acanthopodium*)[20], red fruit (*Pandanus conoideus*) extract[21], and ethanol extract from *Musa paradisiaca L* (MPL) fruit.[22]Regardless of the antimicrobial effect, it has anti-inflammation effects that modulate the immune response. The other example of natural antibiotics is garlic (effective against *Salmonella* and E.coli).[23] Honey (especially Manuka honey)have been reported to exhibit antimicrobial effect against *Staphylococcus aureus* and *Helicobacter pylori* and had been used as an ointment to accelerate wound healing, as well as *Channa striata*.[2425]Echinacea, that has been used for hundreds of years by Native American, have been studied extensively about its role in infectious disease as a model of learning pharmacognosy of the natural product serves as an example in developing the other herbal medicine.[26]

In Indonesia, there are abundant potential herbal resources such as moringa leaf[16],Ajwa dates[27], Channa striata[28]. In the last two decades, the discovery of novel therapeutics to combat multi-drug resistance (MDR) has begun, exclusively with ground plants and deep-sea flora.[29] Biological theories behind these natural products are related to molecular biology, genetics, physiology, and pathology. Food, diseases, poisons, and antidotes have complex interactions that create a wide range of possibilities of their application for secondary metabolites as well as their synthetic or semisynthetic derivatives.[3031]

Phytochemicals have become a source of new molecules that leads to the development of novel drugs with potential immunoregulator and antimicrobial agent used as adjuvant or alternative therapy.[2432]One of the herbal medicines that have promising possible immune regulator effects is Miana. Toraja people in South Sulawesi, Indonesia,uses Miana leaves to treat infectious diseases or boost their immunity.[33] A 2013 survey conducted in the Toraja community of South Sulawesi showed that 85.71% of patients chose to use traditional medicine and apply Miana leaves as the complement of tuberculosis treatment.[34] However, there are no comprehensive reviews on the molecular and immunologic mechanism of Miana in infectious disease. This review will serve as the first extensive study on the molecular mechanism and immune response of Miana in infectious disease as a potential agent for combating infection in years to come.

Search Strategies

A comprehensive search of the literature was conducted in PubMed (NIH), Scopus, EMBASE, Google Scholar, and Portal Garuda database using keyword combinations of the medical subject headings (MeSH) of 'miana', 'iler', 'coleus scutellarioides', 'infection','infectious disease', 'immune response', 'cytokine', 'anti-inflammation','pro-inflammation', and 'transcription factor'.A relevant reference list was also manually searched.

Miana Leaves Extract

Miana is one of the flowering plant species that belongs to the family Lamiaceae. It is native to South East Asia and its neighbouring regions. It is also known *as Coleus blumei* or *Plectranthus scutellarioides*, or *Ocimumscutellarioides*. or *Solenostemons cutellarioides*. The *Coleus* genus contains more than 500 species. Plants need moist-drained soil to grow and typically grow 0.5-1 m, though some may grow as tall as 2 meters. Plants are pretty bushy, woody-based evergreen perennial and mostly grown due to its decorative variegated leaves.[35] In Indonesia, Miana has a rectangular-shaped stem appearance. Their leaves have a triangular-shaped or ovoid shape which colour varies from green to purplish-red. Its flower has a form of stacked strands on its buds with red or white, purple or yellow variations.

Mine are tropical plants that are generally grown as annuals. The various shaped leaves have several colours like chartreuse, rust red, cream, and purple-black. Some cultivars sport almost all of these colours combined. The darker the red spots in the leaves, the more they can tolerate the

sunlight. Miana blooms in the summer. The blue to white nettle like flowers are unremarkable. Thus it tends to detract visually from the impact of the foliage. Miana grows in warm soils with adequate drainage. Miana grown in too much sunlight may wilt. On the side, those grown in too much shade may become leggy.[36]

Miana is one of the plants included in the list of 66 biopharmaceutical crop commodities based on the Decree of the Minister of Agriculture No. 511/Kpts/PD.310/9/2006. The leaves are used by people in the health field such as herbs to treat ophthalmia and dyspepsia, concoctions to reduce swelling in the wound (inflammation), headaches, asthma, coughing, smoothing the menstrual cycle, enhancing appetite, accelerating the maturation of boils, diarrhoea, and worm medicine.[3738] In Toraja ethnic communities (in the province of South Sulawesi, Indonesia), it is one of the medicinal plants which is commonly used.[34]

Miana leaves needs to be extracted. The simplest extraction method is mixing all the ingredients with a solvent, and material will show different solubility in different solvents depending on the polarity of the compound to be extracted so that a pure combination from the plant has medicinal properties.

Miana leaves extraction (MLE) is done by using ethanol, antioxidant compounds such as anthocyanin (pelargonidin-3 routines and cyanidin-3-O-glucoside compounds).Flavonoid compounds play a role in producing antioxidant effects, and this compound will have 5 equilibrium forms depending on the pH conditions, namely cation flavilium, carbinol bases, chalcons, quinonoidal bases, and anionic quinonoidals.[39] The antioxidant activity of ethanol extract of miana leaves is effective in an acidic atmosphere with a citric buffer with citrate-phosphate buffer. Methanol extraction produces compounds such as alkaloids, tannins, flavonoids, saponins and terpenoids. In the chromatograph analysis showed 7 chemical compounds identified in Miana leaf extract, namely (2, 4, 4, 4, 16, 16-D6) -3.alpha., 17.beta.-dihydroxy-5.beta.-androstane, (E,E) - 3,7,11-trimethyl-2,6,10-dodecatrien-1-olacetate, 1,8-Bis (3,4-dicyanophenyl) anthracene, 23-R-methylcholesterol, Stigmasterol, Stigma- 8 (14) - en-3.beta.-ol, and alpha -Amyrin acetate.

The antibacterial mechanism of flavonoids in plants is to inhibit the nucleic acid synthesis and cause damage to the permeability of bacterial cell walls, microsomes, and lysosomes. The mechanism includes interactions between flavonoids and bacterial DNA, forming complex compounds with extracellular proteins, dissolving in the bacterial cell membranes and destroying it, then mixing it with intracellular compounds. Other studies suggest the mechanism of flavonoids inhibits cell membrane function by disrupting the permeability of cell membranes and inhibiting enzyme bonds such as ATPase and phospholipase.[40414243] In 2018Anita et al.[43] conducted a study to determine the flavonoid content of miana leaves. Based on the results of quantitative testing on the levels of miana leaf flavonoids (*Coleus atropurpereus*) that was performed using a UV-Vis spectrophotometer, it showed that an average total flavonoid of 8.59 mg/gram extract was found. Its flavonoids have a relatively high antioxidant activity, namely IC50 the ethanol extract of Miana leaves 48.04 ppm. A study conducted by Khotimah et al. found that IC50 obtained from measurement of antioxidant activity in days 0, 1, 3, 7, and 14 were 70,13 ppm, 57,91 ppm, 50,91 ppm, 48,43 ppm, and 56,10 ppm respectively which were considered very strong antioxidant activity.[1644]

These are the compound that can be obtained from the extraction of miana leaves.[3845]

Flavonoid

Of the various components that can be extracted from miana leaves, flavonoids are the most critical results because they contain oxidant properties. The group of compounds that play a role in eliminating worms and bacteria is known because of the presence of the properties of the group of flavonoid compounds contained therein which can systemically act as immune stimulators that can enhance the body's response to various parasitic and bacterial infections.

Flavonoid also hasan antibacterial mechanism by inhibiting the nucleic acid synthesis and cause damage to the permeability of bacterial cell walls, microsomes, and lysosomes. The interaction between flavonoids and bacterial DNA form complex compounds with extracellular proteins and dissolving them so that they can damage bacterial cell membranes and be followed by intracellular compounds. Other studies suggest the mechanism of flavonoids inhibits cell membrane function by disrupting the permeability of cell

membranes and inhibiting enzyme bonds such as ATPase and phospholipase.[40,42] In 2018, Anita et al. conducted a study to determine the flavonoid content of miana leaves. Based on the results of quantitative testing on the levels of miana leaf flavonoids (Coleus atropurpereus) that was performed using a UV-Vis spectrophotometer, it showed that an average total flavonoid of 8.59 mg extract was found. [42]Its flavonoids have a relatively high antioxidant activity, namely IC50 the ethanol extract of miana leaves 48.04 ppm. A study conducted by Khotimah et al. found that IC50 obtained from measurement of antioxidant activity in days 0, 1, 3, 7, and 14 were 70,13 ppm, 57,91 ppm, 50,91 ppm, 48,43 ppm, and 56,10 ppm respectively which were considered very strong antioxidant activity.[44]

Tanin

The mechanism of action of tannin as an antibacterial is protein agglutination. Tanin has an antibacterial activity related to its ability to activate microbial cell adhesin, activate enzymes, and interfere with protein transport in the inner cell layer. Tanin also has a target on cell wall polypeptides so that the formation of cell walls becomes less perfect.[46,47]

Saponin

The mechanism of action of saponins as an antibacterial is that it can cause leakage of proteins and enzymes from within the cell. Saponins can be antibacterial because the surface-active agents are similar to detergents. As a result, saponins will reduce the surface tension of bacterial cell walls and damage membrane permeability. Saponins diffuse through the outer membrane and vulnerable cell walls and then bind to the cytoplasmic membrane so that it interferes with and reduces cell membrane stability.[48]

Alkaloid

The mechanism of action of alkaloids as an antibacterial is by disrupting the constituent components of peptidoglycan on bacterial cells so that the cell wall layer is not formed intact and causes cell death. Other mechanisms of alkaloid components are known as DNA intercalators and inhibit bacterial cell topoisomerase enzymes.[49]

Steroids

The mechanism of steroids as an antibacterial is related to lipid membranes and sensitivity to steroid components that cause liposome leakage. Steroids can interact with cell phospholipid membranes and cause fragile cell membranes and lysis.[48]The mechanism of steroids as an antibacterial is related to lipid membranes and sensitivity to steroid components that cause liposome leakage.

Alkaloid, steroid, flavonoid, saponin, and tannins are used for antibacterial,and phytols are used for antifungals.[50]Active substances can dilate blood vessels and fibroblasts which act as anti-inflammation.[51]As well as the flavonoid that has anti-inflammation properties.[52]Lastly, quercetin has an antioxidantproperties.[53]

Molecular and Immunology Mechanism of Infectious Disease

Microorganisms such as bacteria that penetrate the epithelial surfaces of the body initially are met immediately by cells and molecules that can mount an innate immune response.[54] Virulence factors play a huge role in stimulating natural immune systems through the pathway of high-mobility group box 1 (HMGB1).[17]There is a plethora of classification of virulence factors which includes exotoxins (secreted by *Corynebacterium diphtheria*, *Vibrio cholera*, and *Clostridium tetani*), modulins such as bacterial lipopolysaccharides which can damage a host by eliciting inflammatory responses and cascades[55], enzymes such as proteases, neuraminidases, and phospholipases [56], attachments such as Gal/GalNAc lectin in *Entamoeba histolytica*, lipoteichoic acids and M protein in *Streptococcus pyogene*s, and flagellae in *Aeromonas* spp.[57]and *E.coli*[58]motility such as actin-based motility to propel themselves forward in *Shigella* spp., *Listeria monocytogenes* and *Rickettsiae* for cell-to-cell spread[59], capsules such as polysaccharide capsules in *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Cryptococcus neoformans,* and *Haemophilus influenzae* which protect microbes from phagocytosis and intracellular killing[60], complement evasion proteins such as C5a peptidase which inhibits leukocyte recruitment from Group A and B streptococci.[61]

AMR facilitatesthe pathogenicity of microorganisms by evading antimicrobial action. There are 2 basic AMR. There wasa genetic and mechanistic mechanism. In genetic, there is a mutation in horizontal gene transfer that plays a role in developing AMR. The mechanistic properties work in the antibiotic molecule,

Table 1. Summary of Studies for Miana Leaf Extract in Vivo/Animal Model

Study	Animal used and exposure	Outcome	Results
Tari et al. 2013 [82]	Rabbit incised on the right and left back	Wound healing	On the day 14, the wound that were given Miana leaves showed faster healing process and shorter wound lengths when compared with control group with difference in the wound lengths varied between 0,5 - 1,1 cm favoring miana leaves.
Marpaung et al. 2014 [51]	Rabbit incised 1,5 cm on the back until subcutaneous tissue and then Staphylococcus aureus bacterial suspension 0.2 mL were given to each location.	Wound healing	On day 8, the wound that were given MLE (SEDM) 20%, 40% and 80% were all already perfectly closed/healed while the wound on gentamycin ointment still have 0.2 - 0.3 cm wound length.
Pakadang et al. 2015 [34]	Adult male Wistar rats infected with Mycobacterium tuberculosis	Number of T-lymphocytes, CD4 T-Cells, IFN-γ and TNF- γ levels	Administration of 510mg/kg BW of EDM to male rats caused a significant increase in T-lymphocyte, CD4 T-Cells proliferation and IFN-γ
Palette et al. 2017 [84]	Mice model infected with Mycobacterium tuberculosis	IL-10 mRNA expression	MLE was able to decrease IL-10 mRNA expression with mean difference (MD) of 0.951 and was statistically significant (P = 0.001)
Karo, 2018 [77]	BALB/c mice Infected with Candida albicans	Fungi load and IL37	Administration of 750 mg/kg BW of EDM to BALB/c mice show similar fungi load suppression and elevation of IL 37 as it compares to Ketoconazole group
Karo, 2018[85]	BALB/c mice infected with Candida albicans	IgM antibody	IgM antibody is decreased in MLE compared to the control group
Syamsuri, 2018 [14]	BALB/c mice infected with Salmonella typhi	mRNA TLR4	Administration of 510 mg/kg BW of Miana to BALB/c suppression of mRNA TLR4 expression
Amsyah, 2018 [83]	Adult Wistar rats infected with A. actinomycetemcomitans	mRNA IL 10	Administration of 510 mg/kg BW of Miana to rats elevate the expression mRNA IL 10

50reased antibiotic penetration and efflux, changes in target sites, and resistance isowing to global cell adaptations.[62]

Inna32mmunity cells respond to various stimuli using pattern-recognition receptors (PRRs) like the Toll-Like Receptors (43Rs) and the NOD-like receptors (NLRs). The pathogen-associated molecular patterns (PAMPs) can be detected by both TLRs and NLRs.at the same time, damage-associated mole35r patterns (DAMPs) can be seen by NLRs. Damage-Associated Molecular Patterns s are molecules that are released from damaged or necrotic host cells which include HMGB1 protein.[63]

NF-êB is 16ecially important in inducing pro-inflammatory genes encoding TNF-á, IL-1â, IL-6, IL-12p40, and cyclooxygenase-2.[64] NF-êB does that with the help of TLR4 to mediate the differentiation of macrophage41owards the M1 phenotype.[65] M1 promotes the production of pro-inflammatory cytokines and the differentiation of inflammatory T cells which both lead to inflammation.[66]In contrast to th19 1 macrophages, the M2 phenotype produces anti-inflammatory cytokines such as IL-10 and IL-13, which are crucial to inhibit inflammation and aid faster-wound healing.[67]

High-mobility group box 1 can amplify the changes in immune response towards multiple organ dysfunction syndromes (MODS) and death. Structures such as TLR2, TLR4, and TLR9 recognize the bacterial structure and HMGB1, including the receptor for advanced glycation end (RAGE) such that bacteria can activate the adaptive immune syst27 Also, TLR4 and HMGB1 interact to activate nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and then the hypoxic inducible factor (HIF)-1á.[6814] NF-êB is 16ecially important in inducing pro-inflammatory genes encoding TNF-á, IL-1â, IL-6, IL-12p40, and cyclooxygenase-2.[64] NF-êB alongside TLR4 helps the differentiation of macrophages towards the M1 phenotype.[65]

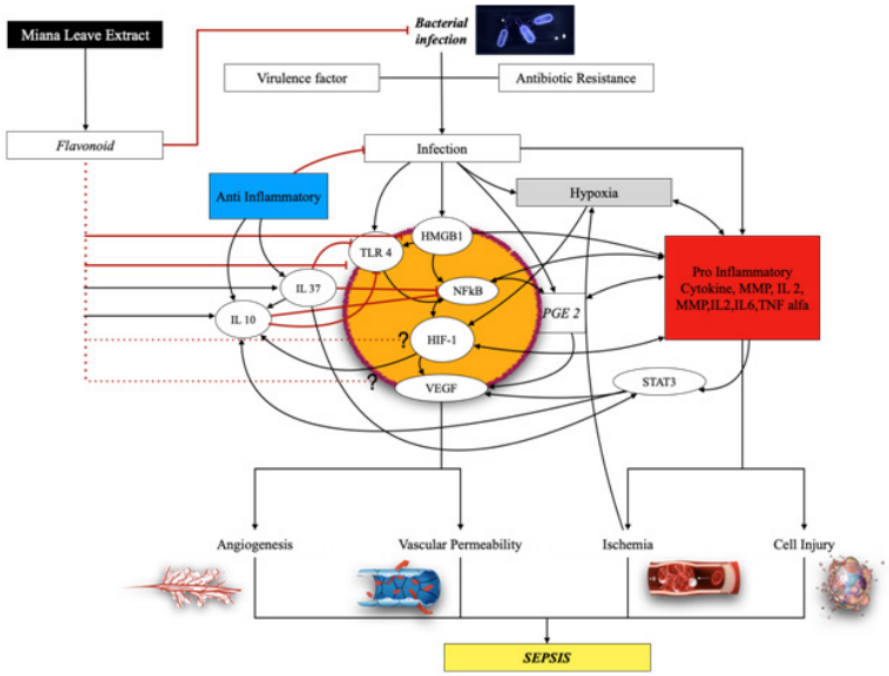

Fig. 1. The mechanism of miana leaf extract in bacterial infection

Upon the onset of infection, pro-inflammatory cytokines such as tumour necrosis factor-á (TNFá), matrix metalloproteinases (MMPs), interleukin 2 (IL-2), and interleukin 6 (IL-6) were produced. TNF-á regulates several critical cell functions, including cell proliferation, survival, differentiation, and apoptosis. Aberrant TNF-á production and TNF receptor signalling have been associated with sepsis.[69]

Host-derived MMPs facilitate leucocyte recruitment, cytokine and chemokine processing, defensin activation, and matrix remodelling, which are essential for pathogen clearance from the host. However, excessive MMP activities may, in turn, lead to tissue damage, favouring pathogen dissemination or persistence, by breaking down barriers to spread or by creating an immune-privileged site that is poorly accessed by host immune cells, therefore causing immunopathology instead.[70]

Interleukin 6 (IL-6) also contributes to aid host defence in times of infection by stimulating acute phase responses, hematopoiesis, and immune reactions. Dysregulated continual synthesis of IL-6 results in pathological conditions of chronic inflammation and autoimmunity.[71]

A unique pathway these cytokines use to activate its action is by communication with signal transducer and activator of transcription 3 (STAT3). STAT3 is a transcription factor activated by many cytokines and growth factors. It plays a crucial role in cell survival, proliferation, and differentiation. Thereby, the Kupfer cells, the ligation of IL-10 with IL-10R1 and IL-10R2 leads to prolonged activation of STAT3, inhibiting inflammatory responses. In contrast, the ligation of IL-6 with IL-6R and gp130, which are expressed at high levels on Kupffer cells, leads to transient activation of STAT3, followed by the induction of inflammatory responses.[72]

Both neutrophils and macrophages have low HIF-1á in an oxygen-rich environment. When recruited to an inflamed site that is relatively hypoxic, the cellular level of HIF-1á is increased and will activate effector pro-inflammatory and bactericidal genes. This increase will induce phagocytotic activities that will be assisted with antimicrobial peptides such as cathelicidins and protein granules with direct antimicrobial activities. Nitric oxide synthase (NOS) which is generated by the increase in HIF-1á will produce nitric oxide (NO) that has antimicrobial properties which in turn will stabilize HIF-1á and enhance innate immunities. The increase HIF-1á levels will ultimately increase the level of vascular endothelial growth factor (VEGF).[73]

Inflammation stimulates the production of cyclooxygenase (COX) 1 and COX 2, which will induce the production of prostaglandin E_2 (PGE2). Prostaglandin E_2 together with HIF-1á, will increase the production of VEGF.[74] Vascular endothelial growth factor, CXCL12, endothelial monocyte activating peptide-II (EMAPII), and Angiopoietin-2 (Ang2) mediate extravasation of monocytes under hypoxic conditions. Moreover, VEGF plays a role in infectious disease by mediating angiogenesis and vasodilation while VEGF works together with histamine to increase vascular permeability during inflammation which causes plasma exudation.[75]

There are anti-inflammatory cytokines that serve to regulate inflammatory reactions such as IL-10 and IL-37. Interleukin-10 inhibits NF-êB by blocking IêB kinase activity and also interferes NF-êB in the nucleus[76] while IL-37 suppresses NF-êB and blocking TLR4 from binding to the host cell.[77] Interleukin-37 is known to promote IL-10 production after cytokine secretion. Moreover, IL-37 upregulated STAT3 expression at genomic and proteomic. IL 37 reduces STAT3 phosphorylation.[78] Interferon-ã is involved in regulating the immune response in autoimmune disease by suppressing the inflammatory response.[79]

Flavonoids in Miana leaf contains antibacterial, antioxidant, and anti-inflammatory effects[1451] in which they increase the T lymphocytes, CD4 T cells, IFN-ã level, and TNF-á.[34] Flavonoids can inhibit bacterial growth and kill microorganisms, especially gram-positive bacteria. The mechanism is inhibiting nucleic acid synthesis, destroying cell membrane, microsomes, and lysosomes, and increase cell permeability resulting in the elimination of the pathogens.[11]Syamsuri et al. in 2018 found that flavonoid has antibacterial activities by suppressing TLR4.[14]

Meanwhile, flavonoid effects on HIF-1á and VEGF are still not apparent. One study found that *homoisoflavone-type methyl ophiopogonanone B* (MOB), a flavonoid compound, is effective in inhibiting HIF-1á and regulating VEGF under hypoxic conditions.[80]

Miana Leaf Extract In Vitro Studies

MLE had a similar antibacterial activity with different concentrations at 80% and 100% concentrations. MLE was sufficient enough to treat a broad spectrum of bacteria, such as *Staphylococcus sp.* and *Streptococcus sp.* to *Escherichia coli* and *Pseudomonas aeruginosa*.[3481]

Leaf Extract In Vivo/Animal Studies

Table 1 summarizes the evidence regarding the benefit of MLE from in vivo/animal studies. Wound healing seems to also benefit from MLE application on the wound. A study by Tari et al.[82] that by the 14th day since the incision, MLE applied to the wound showed a faster healing process and shorter wound lengths when compared with the control group with the difference in the wound lengths varied between 0,5 – 1,1 cm favouring MLE. The wound which was given MLE 20%, 40% and 80% reveals a faster healing rate than gentamycin ointment.[51]

The first animal study of MLE on infection was published by Pakadang et al.2015. The study looked into the effect of MLE on intratracheal infection of *M. tuberculosis* in the Wistar rat model. 510mg/kg BW of EDM were able to increase the proliferation and the activation of CD4 T cells which in turn elevates IFN-ã production at the early stage of tuberculosis infection, leading to immunomodulation of the host.[34]

Another similar study on M. tuberculosis-infected rats found that Miana extract was able to decrease IL-10 mRNA expression. This finding contradicts another study by Amsyah 2018, which found Adult Wistar rats infected with *A. actinomycetemcomitans* experience elevation of mRNA IL-10 when Miana extract was given.[8384]

MLE has another potential immunomodulatory role as it playsan essential effect on IL-37. This was a study in BALB/c mice infected by Candida albicans model. MLE significantly increases IL-37 mRNA expression in the mouse model. The mechanism of action of IL-37 is still not exact, but IL-37 expression has been shown to suppress pro-inflammatory cytokines in experimental animals, it also exerts anti-inflammatory activities. A study by Syamsuri et al. on BALB/c mice infected with *Salmonella typhi* detects suppression of mRNA TLR4 expression, potentially reducing the prevalence of gram-negative infections.[14]

Miana Leaves Extract in Human Studies

To this day, there is no research on human have been published on the effects of MLE treating infectious disease. Therefore, there is plenty of opportunities to investigate its efficacy and safety in human studies.

Future Direction

There are several molecular mechanisms in the immune response that may be modulated by MLE. Firstly, we should investigate the effect of miana in sepsis condition as it compares to the standard antibiotic or its adjuvant role. Secondly, the strategic modulation through HIF-1a activation needs to be investigated whether Miana can alter HIF-1a expression in its role in adjuvant therapy to the antibiotic in infection treatment. Thirdly, the follow-up of cellular and tissue reaction following the expression of VEGF after HIF-1a activation should be explored. Then, we should recognize the active substance in MLE that play a critical role in the intervention. The translation research from animal to human studies need to be conducted immediately. There is a lot more research that needs to be done to explore thetherapeutic mechanism,optimal dosage, side effects, and adverse reaction to make MLE a standard herbal medication.

CONCLUSION

Infectious disease always becomesa health problem. Antimicrobial resistance is a great challenge in managing infectious disease. The role of antibiotics is limited, and the discovery of novel antibiotics has been obstructed in the last decade. The understanding of immune response at the molecular level has created opportunities to enhance the correct immune response. Herbal medicine has been used for ages and empirically show benefit. Miana has demonstrated a potential role in modulating the immune system through enhancing CD 4 cell. Miana increases the production of IL 37 and IL 10 as anti-inflammatory cytokines. Furthermore, Miana alters TLR 4 expression in response to LPS on gram-negative bacteria. Therefore, Miana has a significant potential role in infectious disease management, whether as an alternative or adjuvant to the antibiotic. However, there is plenty of other

molecular mechanisms in various infection model that need to be explored.

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Conflict of Interest

There is no conflict of interest declared.

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