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Review Article

MICROBIAL TRANSLOCATION, TOLL-LIKE RECEPTOR 4, AND *KAEMPFERIA GALANGA* AS NEW PERSPECTIVES IN DENGUE PATHOGENESIS AND THERAPY: A REVIEW

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ABSTRACT

Dengue Virus Infection (DVI) is a major health concern in tropical regions, including Indonesia, with symptoms ranging from mild to severe. Genetic factors, such as Toll-Like Receptor 4 Single-Nucleotide Polymorphisms **(**TLR4 SNPs), influence disease severity. Severe DVI is associated with a cytokine storm and elevated Lipopolysaccharides (LPS), suggesting microbial translocation due to increased intestinal permeability. Antibiotics reduce gut bacterial populations but may worsen permeability. *Kaempferia galanga*, an herbal medicine with antimicrobial and anti-inflammatory properties, presents a potential therapeutic approach. This review explores the role of microbial translocation and Toll-like receptors in DVI pathogenesis and the potential of *Kaempferia galanga* in mitigating these effects. A narrative review was conducted using literature from PubMed, Scopus, and Google Scholar with the keywords "microbial translocation," "TLR4," "*Kaempferia galanga*," "herbal medicine," and "immune modulation" without publication year restrictions. DVI triggers immune cell activation and proinflammatory cytokine production, leading to increased intestinal permeability and microbial translocation. LPS in the bloodstream activates immunocytes via TLR4, amplifying cytokine production and worsening inflammation. While TLR4 SNPs do not directly influence this process, TLR4 expression is involved. *Kaempferia galanga* exhibits antibacterial and anti-inflammatory properties that reduce intestinal permeability, thereby limiting microbial translocation. This, in turn, decreases TLR4 activation by LPS, mitigating the cytokine storm. DVI-induced cytokine production increases intestinal permeability, facilitating microbial translocation and systemic inflammation. LPS activates TLR4, driving cytokine release independently of TLR4 SNPs. *Kaempferia galanga* may inhibit this process through its antimicrobial and anti-inflammatory properties, offering a promising therapeutic strategy.

Keywords: Dengue virus infection, Intestinal permeability, *Kaempferia galanga*, Lipopolysaccharide, Anti-inflammatory herbs

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INTRODUCTION

Dengue virus infection (DVI) is an infection induced by the Dengue Virus (DENV). There are four serotypes of DENV: DENV 1, DENV 2, DENV 3, and DENV 4 [1, 2]. This virus is transmitted to humans via the bites of mosquitoes from the Aedes genus, primarily Aedes aegypti and Aedes albopictus [3–5]. DVI is frequently observed in tropical regions, such as Indonesia, with a spike in cases during the rainy season [1, 2].

Over the past two decades, incidence of DVI have risen dramatically more than eightfold. This rise is coupled by a parallel rise in mortality caused by the disease. Annually, there are from 58 to 96 million cases of symptomatic DVI worldwide, with 250,000 to 500,000 progressing to severe DVI. Annual fatalities due to DVI are estimated between 9,000 and 24,000 individuals [6]. The complexities associated with DVI are anticipated to escalate alongside the rise in cases driven by factors including urbanization [7], population mobility resulting from immigration [8], heightened tourism activities [9], inadequate mosquito vector control strategies [10], and the impacts of global warming [11].

DVI manifests with symptoms including fever, headache, nausea, retro-orbital pain, and hemorrhagic manifestations, which may present as skin rashes, gingival bleeding, or epistaxis. In severe cases, the disease may progress to significant complications, such Dengue Shock Syndrome (DSS) [3–5]. Severe DVI is induced by a cytokine storm that enhances vascular permeability. Consequently, vascular leakage occurs, resulting in hypovolemia, hypotension, shock, and potentially leading up in mortality [12, 13].

Severe DVI has been documented to correlate with elevated concentrations of Lipopolysaccharide (LPS) in the bloodstream. The presence of LPS in the bloodstream results from the translocation of microbes or microbial products from the intestines [14]. This microbial translocation is not linked to bacterial invasion or intestinal hemorrhage but is positively correlated with the degree of vascular leakage [15]. Lipopolysaccharides that enter the bloodstream interact with DENV to induce monocyte cells to generate Platelet Activating Factor (PAF) and several inflammatory mediators [16]. Lipopolysaccharides interact with transmembrane receptors known as Toll-Like Receptor 4 (TLR4) facilitated by LPS-Binding Protein (LBP), Cluster of Differentiation-14 (CD14), and Myeloid Differentiation Factor 2 (MD2). The interaction between LPS and TLR4 initiates the release of Nuclear Factor Kappa β (NF-κB), which enhances cytokine production and contributes to the onset of cytokine storm in severe DVI [17-19].

Several factors contribute to the etiology of severe DVI, which varies among individuals. The factor includes antibody-dependent enhancement, viral pathogenicity, and genetic determinants. Genetic factors, including gene polymorphisms, affect susceptibility to DVI [20]. Single Nucleotide Polymorphisms (SNPs) represent the most prevalent type of genetic diversity in the human genome [21]. SNPs within genes associated with the human immune system improve illness severity [22], such as TLR4 SNPs. Toll-like receptor 4 is a crucial transmembrane protein in the immune system, functioning as a receptor for the recognition of Pathogen-Associated Molecular Patterns (PAMPs) [23]. Activation of TLR4 induces the production of proinflammatory cytokines, which may result in a cytokine storm; thus, persons with SNPs in TLR4 are predisposed to severe DVI.

The spotlight on the cytokine storm mechanism in severe DVI primarily centers on the direct impacts of DENV and the immunological response to this while neglecting other factors, including the involvement of LPS. Cytokine storms resulting from DVI and intestinal leakage, aggravated by TLR4 SNPs, necessitate prompt and adequate treatment. Multiple strategies may be employed, including glucocorticoids, TLR4 inhibitors, antibiotics, and miRNA [24–26]. These therapeutic approaches have not been thoroughly executed and may exacerbate the condition, particularly as miRNA remains in the experimental phase [24].

Together with to current therapeutic approaches, the use of herbs exhibiting g-negative antimicrobial properties and the capacity to mitigate proinflammatory cytokine effects should be evaluated to alleviate cytokine storms in the DVI. Various herbs are known to possess anti-inflammatory and antibacterial effects; however, not all

of them have been traditionally used for the treatment of digestive disorders [27–34]. *Kaempferia galanga* is widely found in Indonesia and has been used as an herbal remedy for digestive disorders [35, 36]. *Kaempferia galanga*, exhibiting dual actions as antibacterial dan antiinflammatgion, may be utilized to mitigate microbial translocation and inhibit cytokine storms in the DVI [37, 38]. This review explores the role of microbial translocation and TLR4 in DVI pathogenesis and the potential of *Kaempferia galanga* in mitigating these effects.

MATERIALS AND METHODS

This review is a narrative literature review aimed at exploring the relationship between microbial translocation, Toll-like receptor 4 (TLR4), and the potential of *Kaempferia galanga* as an immunomodulatory agent. The review process involves the following steps:

Literature search strategy

Relevant literature was collected through searches in electronic databases such as PubMed, Scopus, and Google Scholar. Keywords used included "microbial translocation," "TLR4," "*Kaempferia galanga*," "herbal medicine," and "immune modulation." No strict publication year restrictions were applied to ensure broader theoretical and data coverage.

Selection of literature

Articles were selected based on their relevance to the main topic of the review. Selection involved screening article titles and abstracts to identify studies providing insights into microbial translocation, the role of TLR4, and the pharmacological potential of *Kaempferia galanga*. Review articles, experimental studies, and relevant case reports were included.

Information analysis

Selected literature was critically analyzed to gain a deeper understanding of the relationship between microbial translocation and TLR4 activation, as well as the immunomodulatory effects of *Kaempferia galanga*. The analysis focused on identifying patterns, interconnections, and the contributions of the herbal agent to immune regulation.

Presentation of findings

The findings from the literature were categorized and organized into several main themes: (1) microbial translocation and TLR4 activation, (2) molecular mechanisms of TLR4, and (3) biological activities of *Kaempferia galanga*.

Narrative approach

A narrative approach allowed for a flexible synthesis of information, providing room for broader exploration of conceptual relationships in the context of immunology and herbal therapy.

RESULTS AND DISCUSSION

Microbial translocation

Microbial translocation is frequently observed in patients with severe conditions including Coronavirus Disease 2019 (COVID-19) [39,40], HIV/AIDS [41], cancer [42], sepsis [43], myocardial infarction [44], graft-versus-host disease [45], and autoimmune diseases [46]. The immunological response in these settings results in intestinal leakage or damage to the mucosal layer of the intestine. Both factors promote the translocation of intestinal bacteria or their products into the lamina propria. Microorganisms in the lamina propria compromise the Gut Vascular Barrier (GVB) and/or the Gut Lymph Barrier (GLB). Injury to the GLB permits bacteria to infiltrate the lymphatic system, whereas injury to the GVB allows microbes to reach the circulation via the portal vein [47].

Microbial translocation in DVI

Plasma leakage occurring in dengue virus infection (DVI) leads to hypoperfusion [48]. Intestinal hypoperfusion triggers enterocyte damage, which facilitates the translocation of microbes or microbial products such as LPS into the circulation [49]. However, some reports suggest that microbial translocation in DVI is associated with excessive activation of the immune system [14]. The mechanism of microbial translocation resulting from excessive immune responses remains unclear. Based on existing literature, interleukin-18 is a strong candidate as a key initiator of microbial translocation. However, this hypothesis requires further investigation.

Interleukin-18 is a cytokine that has been found to be elevated in severe cases of dengue virus infection (DVI), both with and without comorbidities [50, 51]. Interleukin 18 is released as a result of inflammasome activation by DENV and the DENV Non-structural 1 (NS-1) protein. IL-18 subsequently initiates the production of ferritin and Interferon γ (IFN-γ) [52, 53]. IL-18 induces microbial translocation through multiple pathways. Initially, Interleukin 18 enhances the production of Myosin Light Chain Kinase (MLCK), which subsequently activates Myosin Light Chain (MLC) via the Rho-Associated Coiled-Coil-Containing Protein Kinase (ROCK) pathway. The activation of MLC draws Zonula Occluden 1 (ZO-1) into the cytoplasm, consequently enlarging the intercellular space and enhancing intestinal permeability [54]. Secondly, Interleukin 18 induces the synthesis of the acute phase protein zonulin, hence enhancing intestinal permeability [55]. Third, IL-18 enhances cellular apoptosis by augmenting the production of caspase-1 and caspase-3. The activation of caspases induces enterocytes apoptosis, subsequently facilitating the translocation of microorganisms and/or their products from the gastrointestinal lumen into the bloodstream [54].

Ferritin, induced by IL-18, is internalized by immunocytes through endocytosis, subsequently activating NF-κB. The activated NF-κB initiates the production of pro-inflammatory cytokines, including IL-1β and TNF-α [56]. Moreover, IL-1β is generated as a result of inflammasome activation by DENV [57]. Interleukin 1β enhances intestinal permeability via multiple methods. Initially, IL-1β promotes the releasing of NF-κB from Inhibitory κB (IκB). Nuclear Factor Kappa B in turn, migrates to the nucleus and promotes MLCK gene expression. The synthesized MLCK protein then activates MLC. The active myosin light chain triggers the redistribution of ZO-1 and occludin, resulting in an increased distance between enterocytes [58, 59]. Secondly, IL-1 β stimulates the Mitogen-Activated Protein Kinase (MAPK) pathway, marked by the activation of Extracellular Signal-Regulated Kinase (ERK) and p38. The ERK protein stimulates the transcription factor Elk-1, whereas p38 activates Activating Transcription Factor 2 (ATF-2). Elk-1 and ATF-2 subsequently translocate to the nucleus to stimulate MLCK gene expression [58, 59]. Third, IL-1β increases the formation of miR-200c-3p, which recognizes mRNA from occludin, thereby stimulating the degradation of occludin mRNA. This causes a decrease in occludin synthesis, thereby disrupting Tight Junctions (TJ) formation. Disrupted TJ cause widening of the gap between enterocytes [60].

Tumor Necrosis Factor α (TNF-α) generated from ferritin endocytosis enhances intestinal permeability [56]. The interaction of TNF-α with its receptor activates Guanine Nucleotide Exchange Factor H1 (GEF-H1), subsequently inducing Rho activation. Rho molecules immediately initiate ROCK activation, which further inhibits Myosin Light Chain Phosphatase, activates MLC2, and stimulates Mammalian Diaphanous-Related Formin (mDia). The activation of MLC2 and mDia increases intestinal permeability by promoting actin farmation and actomyosin contraction [61]. Moreover, TNF-α diminishes the production of tight junction proteins claudin-1 and occludin. Reduced levels of claudin-1 and occludin impair tight junction formation, thereby enlarging the intercellular spaces between enterocytes [62, 63].

IL-18 generated via the inflammasome pathway interacts with IL-12 to induce the secretion of IFN-γ [64]. Furthermore, IFN-γ is generated during Th1 cell polarization in DVI patients [65, 66]. Interferon-γ increases intestinal permeability via several mechanisms. The interaction between IFN-γ and the IFN Receptor (IFN-γR) activates JAK, which then phosphorylates STAT1. The STAT1 molecule subsequently binds to IFN-γR, enabling JAK to recruit and activate STAT5. The STAT5 molecule undergoes phosphorylation and interacts with Fyn. The STAT5/Fyn complex subsequently recruits GRB2-Associated Binder-2 (Gab2) to establish

the STAT5/Fyn/Gab2 complex. The Fyn molecule stimulates Phosphatidylinositol 3-Kinase (PI3K), which is recruited to the STAT5/Fyn/Gab2 complex. The intracellular signaling cascade from PI3K via PDK-1 and PKC promotes intestinal permeability [67]. Secondly, IFN-γ enhances intestinal permeability via the NF-κB/HIF-1α (Hypoxia-Inducible Factor 1α) pathway. IFN-γ enhances the release and translocation of NF-κB into the nucleus, hence beginning HIF-1α production. The synthesized HIF-1α molecules activate MLCK, which then phosphorylates MLC. The phosphorylated myosin light chain subsequently induces the redistribution of ZO-1 and occludin, resulting in the widening of the distance between enterocytes [68, 69]. Third, IFN-γ enhances intestinal permeability via the Rho/ROCK signaling pathway. The interaction of IFN-γ with IFNR activates Rho, thus stimulating ROCK. ROCK molecules enhance intestinal permeability via a mechanism akin to the activation of ROCK by TNF-α [70, 71]. Fourth, IFN-γ stimulates the production of matrix metalloproteinase 9 (MMP9), which degrades claudin-2, 7, and 15. The degradation of claudin compromises tight junctions, as claudin serves to link tight junctions with actin from the cytoskeleton [72]. Fifth, IFN-γ stimulates the production of antimicrobial peptides by intestinal epithelial cells. The generated antimicrobial peptides activate epithelial cells to synthesize complement C3. Pro-inflammatory cytokines are recognized for inducing the synthesis of complement C3, C4, and factor B; however, C5 is yet proven to be generated by pro-inflammatory cytokines, but the intestinal epithelium may generate C5 and C5aR. Complement activation induces the generation of C5a, which is subsequently identified by C5aR. Activation of C5aR then leads to improved intestinal permeability and promotes the production of CXCL8. The chemokine CXCL8 increases neutrophil outflow to the apical region of the intestinal epithelium and promotes the secretion of several complement proteins, hence augmenting complement activation, which eventually elevates intestinal permeability [73–75]. Elevated intestinal permeability facilitates microbial translocation from the intestine into the bloodstream. This results in elevated concentrations of LPS in the bloodstream.

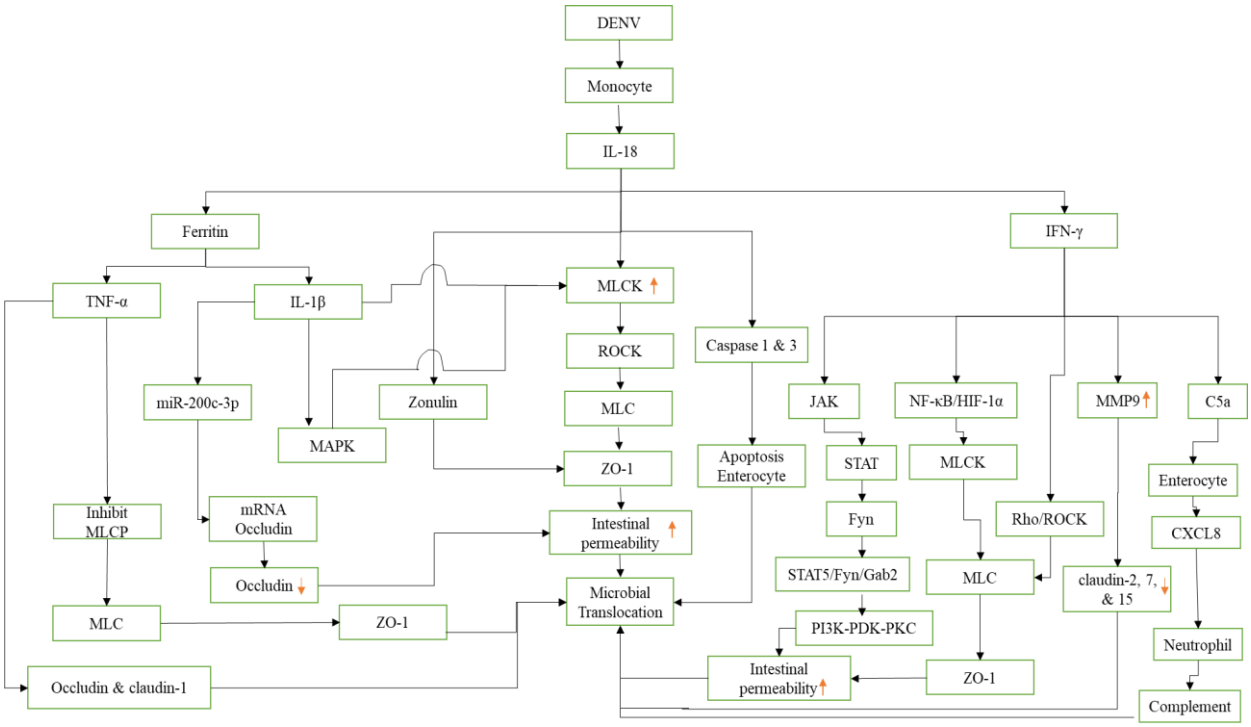

Fig. 1: Schematic representation of microbial translocation due to DVI. Consult the text for a comprehensive description. C5a (Complement 5a), DENV (dengue virus), Gab2 (GRB2-associated binder-2), HIF-1 (Hypoxia-inducible factor 1α), IFN-γ (Interferon γ), IL-1β (Interleukin 1β), IL-18 (Interleukin 18), JAK (Janus Kinase), MAPK (Mitogen-Activated Protein Kinase), mir-200c-3p (MicroRNA 200c-3p), MLC (Myosin Light Chain), MLCK (Myosin Light Chain Kinase), MLCP (Myosin Light Chain Phosphatase), MMP9 (matrix metalloproteinase 9), NF-κB (Nuclear Factor κB), PI3K (phosphatidylinositol 3-kinase), ROCK (Rho-associated coiled-coil-containing protein kinase), STAT (Signal Transducer and Activator of Transcription), TNF-α (Tumor Necrosis Factor α), ZO-1 (Zonula Occluden 1), ↑ (Increase), ↓ (decrease)

TLR4 activation by LPS

TLRs are a group of transmembrane receptors that play a crucial role in the immune system. Humans possess 10 Toll-like receptors, one of which is TLR4. TLR4 is located on chromosome 9q33.1, comprising 3 exons and 2 introns. The role of TLR4 is for recognizing viruses, bacteria, and fungus. The recognition function of TLR4 occurs on the cell surface and within endosomes. Toll-like receptor 4 features three domains: the extracellular Leucine-Rich Repeat (LRR) domain, the transmembrane domain, and the intracellular Toll-Interleukin 1 Receptor (TIR) domain. Activation of TLR4 induces cytokine synthesis by innate and adaptive immune cells. Activation of TLR4 triggers a systemic inflammatory response that may lead to sepsis, organ failure, and septic shock [21].

TLR4 recognizes LPS derived from g-negative bacteria. The identification of LPS by TLR4 is facilitated by LBP, CD14, and MD2. This binding then initiates a cascade of intracellular signaling pathways [17, 18]. The mechanism of TLR activation by LPS can be elucidated through three models. LPS is initially identified by the MD-2 and TLR4 complex, as MD-2 exhibits a strong affinity for LPS, similar to CD14. MD-2 serves to maintain the association of LPS with TLR4. The interaction of LPS with MD-2 or TLR4 induces a conformational alteration in the TLR4 molecule, facilitating TLR4 dimerization. LPS is introduced into the complex with the assistance of CD14 in this state. Secondly, LPS is incorporated into the cell membrane with the assistance of CD14. Additionally, TLR4 and MD-2 interact with LPS, wherein the transmembrane domain of TLR4 recognizes lipid A, whereas MD-2 identifies the head of LPS. The identification of lipid A by TLR4/MD-2 induces alterations in the cell membrane, resulting in the dimerization of TLR with MD-2, which transmits a signal into the cell [76].

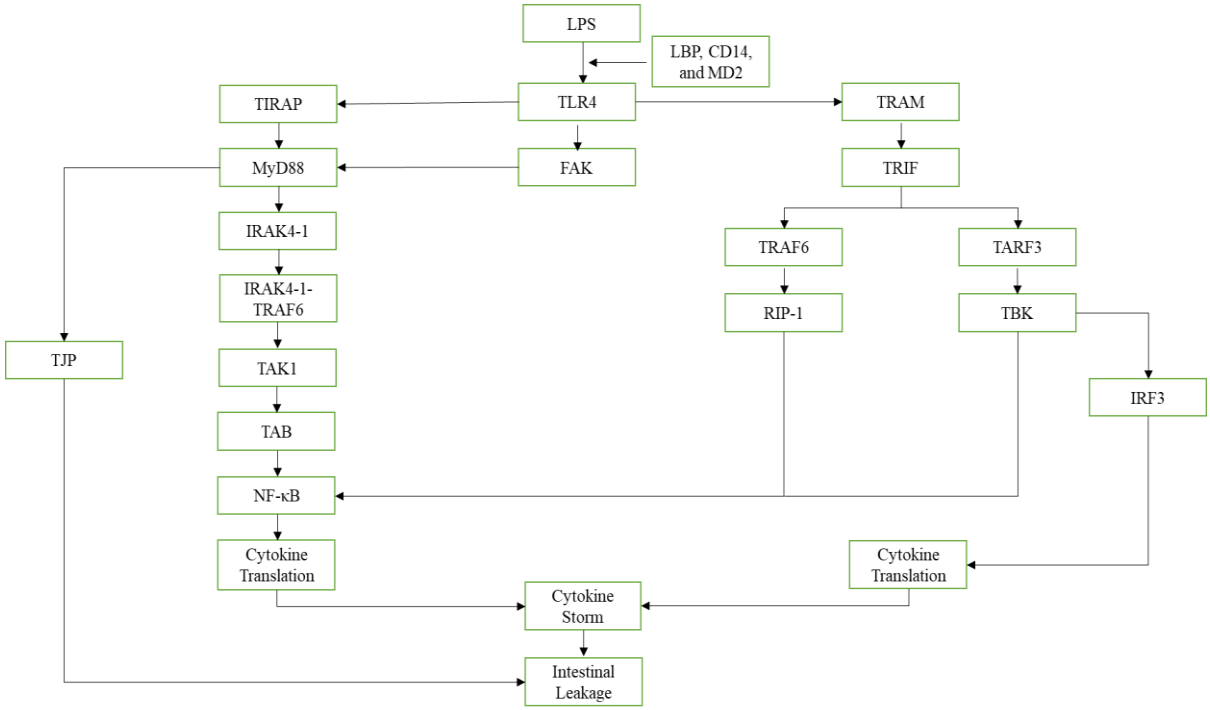

Fig. 2: Schematic representation of the intracellular signaling cascade activated by TLR4 in response to LPS. Consult the text for a comprehensive description. CD14 (Cluster of Differentiation 14), FAK (Focal Adhesion Kinase), IRAK (Interleukin-1 Receptor-associated Kinase), IRF3 (interferon regulatory factor 3), LBP (LPS Binding Protein), LPS (Lipopolysaccharide), MD-2 (Myeloid differentiation factor 2), MyD88 (Myeloid Differentiation Primary Response 88), NF-κB (Nuclear Factor κB), RIP-1 (Receptor Interacting Protein Kinase-1), TAK1 (Transforming Growth Factor β-activated Kinase 1), TBK (TANK-binding Kinase 1), TJP (Tight Junction Protein), TLR4 (Toll-Like Receptor 4), TIRAP (Toll/Interleukin-1 Receptor Domain-Containing Adaptor Protein), TRAF (Tumor Necrosis Factor Receptor-Associated Factor), TRAM (TRIF-Related Adaptor Molecule), TRIF (TIR Domain-Containing Adaptor-Inducing Interferon-β)

The interaction of LPS with TLR4 promotes TLR4 oligomerization and the recruitment of adaptor proteins via its TIR domain interaction. The TIR domain interacts with five adaptor proteins: MyD88, TIRAP, TRIF, TRAM, and SARM. The TLR4 contact signal can occur via a MyD88-dependent pathway involving the adaptor proteins TIRAP and MyD88, or by a MyD88-independent mechanism, also known as the TRIF-dependent pathway, which involves the adaptor proteins TRAM and TRIF. In the MyD88-dependent pathway, TIRAP functions as an adapter for MyD88, facilitating its recruitment to the TLR4 domain in the cytoplasm, where it subsequently interacts with IRAK4 and IRAK1 via the homophilic death domain (DD) [77].

The altered IL-1 receptor-associated kinase is then released from MyD88 into the cytoplasm. The IL-1 receptor-associated kinase subsequently associates with TRAF6 (Tumor Necrosis Factor Receptor-Associated Factor 6). Furthermore, TRAF6, together with the ubiquitin E2 enzyme complex (UBC13 and UEV1A), initiates the polyubiquitination of TRAF6 and TAK1 (Transforming Growth Factor β-Activated Kinase 1). The TAK1 protein associates with the regulatory subunits TAB1, TAB2, and TAB3. Upon complex formation with the regulatory subunits, TAK1 next activates two distinct signaling pathways. The two pathways are the IκB Kinase (IKK)–NF-κB complex pathway and the IKK-MAPK complex pathway. Additionally, TAK1 associates with the IKK complex, which comprises IKKα, IKKβ, and the NF-κB essential modulator (NEMO), via the ubiquitin chain. The IKK complex phosphorylates the NF-κB inhibitor IκBα, leading to its degradation, which then releases and activates NF-κB. Nuclear factor κB subsequently translocate to the nucleus. The binding of NF-κB to the promoter of the gene that encodes proinflammatory cytokines initiates gene transcription, resulting in the production of Messenger RNA (mRNA). The synthesis of mRNA will be succeeded by its translation in the ribosome, resulting in the production of proinflammatory cytokine proteins. Transforming growth factor β-activated kinase 1 also activates the MAPK signaling pathway, so initiating the inflammatory response [18, 78, 79].

In the MyD88-independent pathway (TRIF-dependent pathway), TRAM is used only by TLR4 and serves as a bridge for the MyD88-independent pathway to recruit TRIF to TLR4 [77]. TRIF utilizes TRAF6 and TRAF3 to activate further signaling pathways. The TRAF6 protein binds with Receptor Interacting Protein Kinase 1 (RIP-1) to create a complex that activates NF-κB, whereas TRAF3 activates IKK-related kinases TANK-Binding Kinase 1 (TBK1) and IKKi. Furthermore, active TBK1 and IKK1 phosphorylate IRF3 and activate NF-κB. The phosphorylated IRF3 protein translocates to the nucleus to commence gene expression. The activation of NF-κB and IRF3 necessitates the facilitation of Pellino-1 through three mechanisms [18, 78].

The role of LPS in increasing intestinal permeability

In physiological situation, LPS in the intestinal lumen increases intestinal Tight Junction Protein (TJP) via stimulating the expression of TLR4 and CD14 on enterocyte cells. The interaction of LPS with TLR4 initiates intracellular signaling cascades. The TLR4 signal constitutes a MyD88-dependent pathway that improves intestinal permeability since the lack of MyD88 inhibits the augmentation of TJP, although the presence of TRIF and TRAF does not influence the rise in TJP. This demonstrates that the elevation of TJP produced by LPS is regulated by a MyD88-dependent pathway [77].

The elevation of TJP and intestinal inflammation are regulated by the TLR4 activation complex on the FAK (focal adhesion kinase) protein and the activation of FAK on MyD88/IRAK4, excluding the TRIF/TRAM pathway. FAK is a protein tyrosine kinase that operates downstream of integrin signaling and can initiate inflammatory reactions. FAK is recognized as an adapter protein that participates in the TLR4 signal transduction pathway, facilitating inflammatory reactions. Furthermore, FAK participates in the phosphorylation and transcriptional activity of NF-κB in endothelial cells. FAK inhibition or silencing obstructs LPS-induced MyD88 activation on TJP. FAK activation results from the LPS-TLR4 binding complex, which activates MyD88 and IRAK4. Consequently, FAK is pivotal in

facilitating TLR4 activation via the MyD88 pathway to increase TJP. *In vivo* investigations established that the high dose LPS induced elevation in intestinal permeability in mice and correlated with the activation of FAK and MyD88 [77, 80].

The role of LPS in the onset of cytokine storms in DVI

TLR4 activation by LPS increases the releasing of proinflammatory cytokines such as IL-1, IL-6, TNF-α and triggers a cytokine storm [17–19].

Activation of TLR4 by intestinal LPS promotes the synthesis of proinflammatory cytokines, including IL-1β. These cytokines stimulate epithelial cells to synthesize CXCL7, which is chemotactic for neutrophils [81]. Neutrophils that infiltrate sub-epithelial tissue contribute to inhibit microbial translocation by phagocytosing bacteria, generating reactive oxygen species, synthesizing antimicrobial peptides, and creating neutrophil extracellular traps. Nonetheless, if this procedure is excessive, it may induce inflammation and intestinal damage [82]. This exacerbates the cytokine storm and increases intestinal permeability.

In DVI, elevated levels of High Mobility Group Box 1 (HMGB-1) are associated with disease severity [83, 84]. This transpires as LPS stimulates monocytes to secrete HMGB-1 via a mechanism reliant on the P300/CREB-Binding Protein-Associated Factor (PCAF) acetylase complex (85)]. Upon exiting the cell, HMGB-1 can associate with the Receptor for Advanced Glycation End Products (RAGE), TLR2, and TLR4. Upon binding of HMGB-1 to its receptor, the release of NF-kB is initiated, along with the activation of IRF3 and AP-1, facilitating the translocation of these three factors into the nucleus to induce the transcription of genes encoding proinflammatory cytokines (such as TNF-α and IL-6) and genes encoding IFN. This mechanism results in an elevation of circulating cytokines, therefore facilitating the onset of a cytokine storm [86-88]. HMGB-1 levels elevate in response to the synergy between reactive oxygen species, proinflammatory cytokines, and protein C from DENV in conjunction with lipopolysaccharides. Indeed, HMGB-1 released alongside LPS induces immunocytes to generate increased cytokine levels [89, 90].

Significance of TLR4 polymorphisms on DVI cases

The TLR4 domain responsible for binding to LPS is the extracellular LRR, which exhibits the highest genetic variation, despite the frequency of such variation in the human population being less than 1%. The LRR functions in the recognition of PAMPs, so the genetic variation observed is a consequence of exposure to diverse pathogens [91]. TLR4 is involved in the detection and identification of many pathogenic microbial components. The primary target of TLR4 ligands is LPS, a component of the outer membrane of g-negative bacteria. The polymorphisms 896 A>G and 1196 C>T in the extracellular domain of TLR4 alter the functionality of the TLR4 gene in detecting PAMPs [92].

The reported TLR4 gene polymorphisms are non-synonymous, notably SNP rs4986790 (Asp299Gly/896 A>G) and rs4986791 (Thr399Ile/1196 C>T), each occurring in over 5% of the population [91–93],-2570 A>G, and-2081 G>A [92]. In SNP rs4986790, an A/G base substitution occurs at base position 896 (896A/G), resulting in the alteration of aspartic acid to glycine. In SNP rs4986791, a C/T base substitution leads to a change of threonine to isoleucine, thereby affecting the protein-coding function (missense) [21, 91]. Polymorphisms in TLR4 significantly influence the recognition of pathogens, hence affecting a determination of risk and the defense against infectious diseases [21]. The presence of both polymorphism types affects TLR4's responsiveness to bacterial endotoxins. Individuals with Asp299Gly and/or Thr399Ile polymorphisms have impairments in their response to LPS [91].

The North Indian population exhibited that the Asp/Gly and Thr/Ile genotypes presented a heightened risk of dengue virus infection relative to persons with homozygous genotypes. A notable correlation existed between the Asp/Gly and Thr/Ile genotypes and dengue infection. Analysis of allele frequencies for both SNPs revealed the presence of the Gly allele (Asp/Gly) and the Ile allele (Thr/Ile) in dengue patients relative to control persons. Polymorphisms in TLR4 impact signaling pathways and influence host immunological responses; the Gly and Ile haplotype enhances susceptibility to dengue virus infection (P=0.042 and P=0.024, respectively), but it is not related to the dengue severity [94]. Investigations within the Indonesian population indicated that pediatric dengue patients exhibiting severe clinical manifestations (DHF/DSS) were not correlated with the Asp299Gly and Thr399Ile polymorphisms (P=0.400), consistent with findings from research performed in North India [93]. The study indicated that TLR4 mRNA expression in severe cases (DHF/DSS) was reduced compared to moderate dengue infections (DF). Consequently, it may be inferred that distinct pathogenic processes exist between DHF/DSS and DF, with SNPs in TLR4 posing a greater risk factor for DF than for DHF/DSS [94].

Several studies across European, Asian, and African populations have demonstrated no correlation between TLR4 polymorphisms and disease susceptibility. Establishing the correlation between the Asp299Gly/Thr399Ile haplotype and phenotype, as well as its influence on susceptibility to g-negative bacterial infections, is complex due to the three methodological approaches in TLR4 research: genetic association studies, functional stimulation experiments, and the cloning and transfection of mutated TLR4. Most genetic association studies indicate no correlation between the TLR4 Asp299Gly/Thr399Ile haplotype and disease vulnerability. The other two methodologies indicated that the TLR4 Asp299Gly/Thr399Ile haplotype influences the phenotype and diminishes cytokine production in the innate immune response, as evidenced by a reduction in NF-κB activity in cells transfected with the TLR4 haplotype compared to normal TLR4. However, this transfection measurement fails to provide a comprehensive view of the phenotype as a complete system since transfection only represents homozygotes, while the majority of studies examining the relationship between genetic associations and function include heterozygous TLR4 haplotypes due to the rarity of homozygous polymorphisms [91]. The existing literature indicates that although SNPs are believed to influence disease processes, there are few reports demonstrating a strong association between SNPs and the severity of dengue virus infection [95].

The outcome of DENV infection is influenced not only by host genetic factors but predominantly by the genetic determinants of the virus (the genotype of the infecting strain) and comorbid factor. All DENV subtypes have been identified in both India and Indonesia. The strains DENV-1III, DENV-1V, DENV-2II, and DENV-3I are predominantly found in India, whereas DENV-1IV, DENV-2II, DENV-3III, DENV-4II, and DENV-4I are more frequently detected in Indonesia [96]. All DENV serotypes are associated with severe DVI. However, the cosmopolitan genotype of DENV-2 is the strain most frequently linked to severe DVI [96–104]. This is attributed to the fact that DENV2 cosmopolitan genotype induces a high viral load [105]. Meanwhile, comorbidities such as hypertension and diabetes mellitus are commonly observed in both India and Indonesia [106–109]. These conditions may predispose individuals to severe DVI due to pre-existing inflammatory states and endothelial dysfunction, which facilitate plasma leakage [51, 110, 111]. Consequently, genetic studies that neglect this aspect risk yielding false negatives. Nonetheless, a minority of individuals infected with DENV exhibit that host genetic factors can impact disease outcomes. Factors elucidating the relationship between host genetics and DENV infection outcomes include comparative studies among ethnic groups, blood types, and Human Leukocyte Antigen (HLA) polymorphisms. This indicates that DENV strains exhibit differing levels of virulence, rendering certain DENV genotypes more pathogenic than others [112]. The interplay of multiple variables induces a cytokine storm that may result in severe DVI. Patients experiencing severe DVI are at danger of multiple organ failure and mortality [113].

Reducing microbial translocation and decreasing inflammation attenuates the cytokine storm

Elevated LPS levels in DVI patients are recognized to originate from microbial translocation. Mitigating microbial translocation from the intestine to the bloodstream is crucial for decreasing morbidity and death in DVI patients. The use of antibiotics, cytokine inhibitors, and the prevention of intestinal hemorrhage are crucial in preventing microbial translocation [24–26].

Historical evidence indicates that antibiotics inhibit microbial translocation [114]. Furthermore, the treatment of the antibiotic meropenem inhibits the translocation of Pseudomonas from the intestine [25]. The antibiotic rifaximin has been shown to prevent microbial translocation in patients with liver disease [115, 116]. These facts provide an adequate basis indicating that antibiotic therapy can mitigate microbial translocation. One of the main advantages of using antibiotics for this purpose is their rapid onset of action and the availability of standardized dosing [117, 118]. Nonetheless, the administration of antibiotics has inherent risks. Evidence indicates that antibiotic administration induces dysbiosis [119, 120] and lowers the production of Short-Chain Fatty Acids (SCFA) by intestinal microflora [121, 122]. *Kaempferia galanga* has the ability to modulate the gut microflora, leading to an increased abundance of SCFA-producing bacteria. [123]. The SCFAs produced enhance the synthesis of occludin, which strengthens the tight junctions between enterocytes (124). This makes *Kaempferia galanga*, which possesses antibiotic properties, a promising candidate for adjunctive therapy alongside conventional antibiotics.

A cytokine storm occurs in DVI, leading to intestinal permeability; thus, the administration of cytokine inhibitors decreases microbial translocation [24, 125]. The high cost of cytokine inhibitors complicates their implementation [126], whereas DVI predominantly proliferates in equatorial regions, which are typically economically poor [127].

DENV stimulates inflammasomes to produce proinflammatory cytokines IL-1β and IL-18 [57]. Proinflammatory cytokines correlate with increased intestinal permeability [128]. The occurrence of elevated intestinal permeability in DVI leads to microbial translocation, exacerbating the cytokine storm as previously elucidated. Inhibiting inflammation will diminish microbial translocation and alleviate the cytokine storm.

The antibacterial, anti-inflammatory, and mucosal-protecting effects of *Kaempferia galanga* as an adjunct therapy in DVI

Diverse therapeutic approaches have been employed to address cytokine storms and heightened intestinal permeability. To date, no pharmacological agent or therapeutic approach has been proven to be fully effective in addressing increased intestinal permeability without adverse side effects [129]. Further development of treatments is necessary, using natural substances with antibacterial and anti-inflammatory effects, such as *Kaempferia galanga*.

Kaempferia galanga is a species member to the Zingiberaceae family from the genus *Kaempferia*. *Kaempferia galanga*, referred to as kencur in Indonesia, is prevalent and utilized as both a culinary spice and medicinal herb in Asia [36]. Its aromatic rhizome has traditionally served as a culinary spice, a component in cosmetic formulations, a natural fragrance, and a flavoring agent. Traditionally, *Kaempferia galanga* has been used for a wide range of medicinal purposes, including treatment. The use of *Kaempferia galanga* as an herbal remedy has a long-standing tradition in various cultures. Traditionally, *Kaempferia galanga* has been employed for a wide range of medicinal purposes, including the treatment of whooping cough, mouth ulcers, and rheumatism, as well as for managing dandruff, diarrhea, and intestinal wounds. It has also been used to alleviate body aches, hematemesis, digestive disorders, and menstrual pain. Other traditional applications include treating tongue blisters in infants, toothaches, and sore throats, as well as functioning as a stimulant, expectorant, and antipyretic. Furthermore, *Kaempferia galanga* is believed to be effective in addressing baldness, ear inflammation in children, the common cold, headaches, and flatulence, and it has been utilized as a diuretic, carminative, and antidote for snake venom [130]. The use of KG as an anti-infective and anti-inflammatory agent is further discussed in the following subsection.

The *Kaempferia galanga* plant features rhizomes, stems, leaves, and flowers. The rhizome is the most commonly utilized component in traditional medicine [131]. *Kaempferia galanga* comprises 97 components categorized into terpenoids, phenolics, cyclic dipeptides, flavonoids, diarylheptanoids, fatty acids and esters, and polysaccharides [36, 132, 133].

In vitro antimicrobial studies of *Kaempferia galanga* demonstrate its antimicrobial efficacy against g-negative bacteria (*Escherichia coli, Salmonella typhimurium*) and g-positive bacteria [38, 134, 135]. *Kaempferia galanga* essential oil at a concentration of 1% inhibited the growth of *Streptococcus pyogenes* and *Staphylococcus aureus* bacteria [134]. The ethanol crude extract at a concentration of 200 mg/ml inhibited the growth of *Lactobacillus sp.* with an inhibition zone diameter of 11.56±0.53 mm, *Escherichia coli* (9.67±0.79 mm), and *Staphylococcus aureus* (10.78±0.91 mm), whereas the ethyl acetate extract at the same concentration (200 mg/ml) inhibited *Lactobacillus sp*. (16.22±0.14 mm) and *E. coli* (14.34±0.08 mm) [135]. Ethyl p-methoxy cinnamate, ethyl cinnamate, and acetic acid facilitate the antibacterial properties of *Kaempferia galanga* [36, 38, 134]. The 2,4-dihydroxybenzoic acid solution derived from *Kaempferia galanga* at a concentration of 100 ppm inhibited the growth of *Escherichia coli* and *Vibrio alginolyticus* [136]. The active compound in *Kaempferia galanga* disrupts the bacterial cell membrane, resulting in the leakage of cellular contents. Compromise of the bacterial cell membrane facilitates the ingress of active chemicals and amplifies the lethal efficacy, resulting in bacterial cell death [137].

Kaempferol and flavonoid Ethyl-p-methoxycinnamate, both phenolic substances, exhibit anti-inflammatory properties. Kaempferol at a concentration of 50 μM inhibits IL-6 production in mast cells stimulated by lipopolysaccharide (LPS) [138]. An *in vitro* study using macrophage cells demonstrated that treatment with Ethyl-p-methoxycinnamate at concentrations of 200, 400, and 800 mg/kg inhibited IL-1 synthesis by 11.35%, 20.9%, and 37.67%, respectively. At the same concentrations, Ethyl-p-methoxycinnamate also inhibited TNF-α synthesis by 24.43%, 37.95%, and 57.40%, respectively [139]. *In vitro* research shows that Ethyl-p-methoxycinnamate at concentrations of 125, 250, and 500 μM reduces viral production by 32%, 16%, and 1%, respectively. Furthermore, Ethyl-p-methoxycinnamate at a concentration of 500 μM was the most effective in reducing the synthesis of IL-6, TNF-α, RANTES, and IP-10. Inhibition of cytokine and chemokine formation occurs because Ethyl-p-methoxycinnamate inhibits the release of NF-κB [140]. Reduced generation of proinflammatory cytokines mitigates cytokine storms and limits increased intestinal permeability [141, 142]. Although *Kaempferia galanga* has been shown to reduce cytokine synthesis, its effect on the function of TLR4 SNPs remains unknown; therefore, further research is needed to clarify this issue.

The NS1 protein of DENV signifies elevated viral load and serves as a marker for severe DVI [143]. The NS1 protein induces the synthesis of prostaglandins [22]. Elevated prostaglandin levels signify the activity of the Cyclooxygenase-2 (COX-2) enzyme. COX-2 and prostaglandins promote DENV replication [144]. The replication of DENV induces a significant viral burden linked to the production of pro-inflammatory cytokines. Pro-inflammatory cytokines induce a cytokine storm and elevate the risk of intestinal permeability. Both can be suppressed by COX-2 inhibitors. Extracts of ethyl alcohol and ethyl acetate at a concentration of 96% from *Kaempferia galanga* reduce inflammation by 79.99% [145]. Moreover, *Kaempferol* is recognized for its anti-inflammatory properties by obstructing the synthesis of prostaglandins via the COX-2 enzyme [146]. Considering these investigations, *Kaempferia galanga* might be useful as a DVI treatment. The limitation of this study is the lack of scientific articles on research regarding the use of *Kaempferia galanga* in patients with DVI. As a result, although the conclusions drawn are highly promising, they may not necessarily reflect actual findings in DVI patients.

Kaempferol and luteolin, phenolic substances found in *Kaempferia galanga*, provide beneficial properties for the mucosal barrier. The administration of an alcoholic extract from *Kaempferia galanga* rhizomes, which contains kaempferol and luteolin at concentrations of 3713 μg/g and 2510 μg/g, respectively, resulted in a reduction of gastric ulcers by 13.42% and 11.65% [147]. This represents a novel opportunity to mitigate elevated intestinal permeability in DVI. Genetic variation in TLR4 has not been shown as a risk factor for DVI. This study highlights the need to consider *Kaempferia galanga* as a complementary therapy for DVI, especially given the availability of *Kaempferia galanga* in the form of effervescent tablets [148].

Despite *Kaempferia galanga* possesses antimicrobial and anti-inflammatory properties, the optimal dosage for its use in preventing microbial translocation in dengue virus infection (DVI) remains unknown. Therefore, further research is needed to determine the appropriate dosage and therapeutic effects of *Kaempferia galanga* in DVI patients.

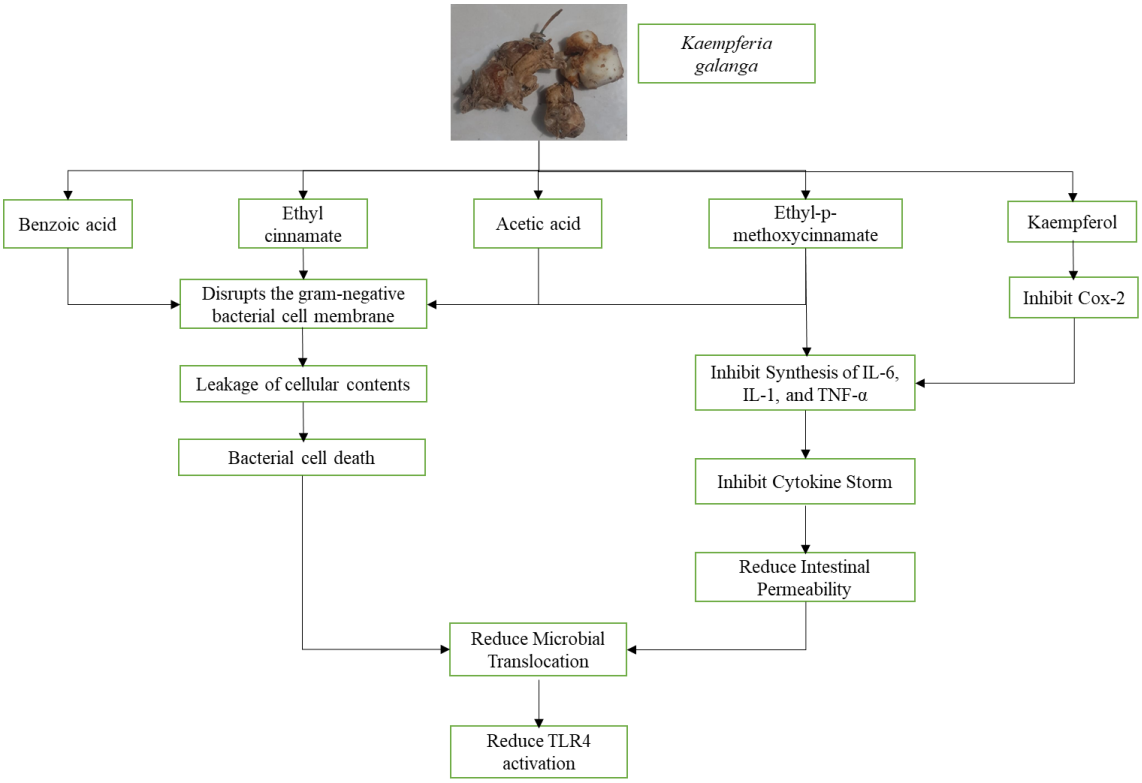

Fig. 3: Illustration of the antibacterial and anti-inflammatory properties of *Kaempferia galanga*. Consult the text for a comprehensive description. Cox-2 (Cyclooxygenase-2), IL-1 (Interleukin 1), IL-6 (Interleukin 6), TNF-α (Tumor Necrosis Factor α)

CONCLUSION

Cytokine production triggered by DVI enhances intestinal permeability, promoting microbial translocation and systemic inflammation. Microbial translocation increases LPS levels. LPS interacts with TLR4, stimulating cytokine release regardless of TLR4 SNP variations, further exacerbating inflammation. *Kaempferia galanga* possesses antimicrobial and anti-inflammatory properties that may help regulate this process, presenting a potential therapeutic approach.

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AUTHORS CONTRIBUTIONS

SWJ and RA jointly conceived the idea and scope of this narrative review. SWJ conducted the literature search, analyzed relevant studies, and drafted the initial manuscript. Riandini Aisyah contributed to data interpretation, manuscript refinement, and critical revisions for intellectual content. Both authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

CONFLICT OF INTERESTS

Declared none

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