RESEARCH PAPER

Averrhoa Bilimbi Linn Leaves as a Potential Antiinflammatory Agent: A Comprehensive Review of Efficacy, Safety, and Mechanism

Hazlianda CP[1*], Pane YS[2], Lubis RDS[3], Rambe AYM[4], Djawad K[5], Laksmi LI[6], Amin MM[1,7] and Restimulia L[4]

[1]Philosophy Doctor in Medicine Program, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[2]Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[3]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[4]Department of Otorhinolaryngology - Head and Neck Surgery, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[5]Department of Dermatology and Venereology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[6]Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[7]Department of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
*[*]**Corresponding author:** Dr. Cut Putri Hazlianda, M.Ked(DV), Sp.DVE, Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara*
Email: cut.putri@usu.ac.id

Received: 28th Feb, 2026; Revised: 6th March 2026; Accepted: 7th April, 2026; Available Online: 20th April, 2026

ABSTRACT
Inflammation is a complex response to tissue injury caused by factors such as infection, trauma, and environmental stressors. Plant-derived phytochemicals have gained attention as potential anti-inflammatory agents. This literature review evaluates the anti-inflammatory properties of Averrhoa bilimbi Linn using sources from PubMed and Google Scholar. The plant, widely used in traditional medicine, contains bioactive compounds with analgesic, antioxidant, and anti-inflammatory effects. Its leaf extracts inhibit key inflammatory mediators, including prostaglandin E2 and TNF-α, and reduce oxidative stress. Mechanisms may involve suppression of cytokines and IgE production. Overall, Averrhoa bilimbi Linn shows promising potential as a natural anti-inflammatory therapy.
Keywords: Averrhoa bilimbi Linn, herbal medicine, anti-inflammatory, alternative.
How to cite this article: Hazlianda CP, Pane YS, Lubis RDS, Rambe AYM, Djawad K, Laksmi LI, Amin MM, Restimulia L, Averrhoa Bilimbi Linn Leaves as a Potential Antiinflammatory Agent: A Comprehensive Review of Efficacy, Safety, and Mechanism. Int J Drug Deliv Technol. 2026;16(6): 563-570. DOI: 10.25258/ijddt.16.6.93
Source of support: Nil.
Conflict of interest: None

1. INTRODUCTION

Inflammation is a complex biological response to tissue injury caused by trauma, infection, environmental factors, toxic chemicals, or overuse. It is characterized by classic signs such as warmth, pain, edema, erythema, and loss of function. Both cellular and humoral immune mechanisms regulate this process. Increased production of reactive oxygen and nitrogen species (ROS and RNOS), which can damage DNA, is closely associated with inflammation.[1] Common inflammatory biomarkers include cytokines such as tumor necrosis factor-α (TNF-α), interleukins (IL-1, IL-6, IL-8), and monocyte chemotactic protein-1, as well as enzymes and proteins like cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), C-reactive protein (CRP), matrix metalloproteinases (MMP), and vascular endothelial growth factor (VEGF).[2] Failure to resolve inflammation can lead to chronic inflammatory diseases, emphasizing the need for effective therapeutic strategies, including herbal medicine.[3]

Herbal medicine, one of the oldest healing systems, uses plant materials to treat diseases and promote health. The World Health Organization (WHO) reports that approximately 80% of the global population relies on herbal medicine for primary healthcare, partly due to the adverse effects of conventional drugs.[4] Plant-derived bioactive compounds have gained attention for their antioxidant and anti-inflammatory properties, supporting oxidative balance and enhancing therapeutic efficacy while minimizing toxicity.[5] Advances in extraction and isolation techniques have enabled the identification of numerous active constituents used clinically to treat conditions such as cardiovascular diseases, obesity, cancer, diabetes, and chronic inflammation.[6–8]Para-inflammation, or chronic low-grade inflammation, represents an intermediary phase between baseline homeostasis and inflammatory conditions, triggered by tissue stress or dysfunction via tissue-resident macrophages. Prolonged exposure to stressful conditions

**Author for Correspondence: cut.putri@usu.ac.id*

may lead to the progression of para-inflammation into a chronic state. Many human diseases are linked to systemic chronic inflammatory disorders resulting from the dysregulation of para-inflammation. Phytochemicals derived from plants have emerged as innovative agents for the prevention of chronic inflammation.[8]

Chronic low-grade inflammation (para-inflammation) arises from prolonged tissue stress and can progress into systemic inflammatory disorders. Phytochemicals offer promising preventive and therapeutic potential in this context.[8] One notable plant is *Averrhoa bilimbi* Linn (Belimbing Wuluh), widely found in Indonesia. All parts of the plant exhibit medicinal properties, particularly anti-inflammatory effects.[9] This study reviews the anti-inflammatory potential of *Averrhoa bilimbi* leaves, focusing on their efficacy, safety, and mechanisms of action, while addressing gaps between traditional use and scientific validation.

2. MATERIALS AND METHODS

This literature study aimed to collect, assess, and synthesize pertinent papers, on the anti-inflammatory properties of *Averrhoa bilimbi* Linn leaf. Scientific databases such as PubMed and Google Scholar were searched to retrieve peer-reviewed articles, clinical studies, and relevant scientific reports. Keywords used in the search included "*Averrhoa bilimbi Linn*," "anti-inflammatory," "phytochemicals," "medicinal plants," "traditional medicine," and "safety profile." Inclusion criteria comprised studies published in peer-reviewed journals, focusing on the anti-inflammatory effects of *Averrhoa bilimbi* or its bioactive compounds, and written in English. Exclusion criteria included studies lacking relevant data, non-scientific sources, and review articles without original research. Only publications from the past five years were considered to ensure up-to-date findings. Extracted data included study methodology, key results, identified bioactive compounds, and safety evaluations.

3. RESULTS

Overview of Inflammation and Its Treatment Challenges

Inflammation is primarily triggered by the innate and adaptive immune systems in response to infection, serving as a protective mechanism against harmful environmental stimuli and chemicals. It plays a crucial role in tissue repair, self-healing, and defense against pathogens. However, excessive or prolonged inflammation can be detrimental, as inflammatory substances may damage cells, cause necrosis, and impair metabolic and immune functions, ultimately leading to tissue injury and organ dysfunction.[10],[11]

Inflammatory mediators are chemical substances produced by body fluids or secreted by cells during inflammation. Key mediators include prostaglandins, nitric oxide, cytokines (e.g., IL-1β, IL-2, IL-6, IL-8), and chemokines. Activation of toll-like receptors (TLRs) stimulates the release of pro-inflammatory cytokines such as TNF-α and IL-6, along with signaling pathways like nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), which regulate immune responses and cellular proliferation. Cytokines are classified as pro-inflammatory (e.g., TNF-α, IL-1β) or anti-inflammatory (e.g., IL-10), maintaining the balance of the inflammatory process.[10]

Anti-inflammatory peptides act by inhibiting NF-κB and MAPK pathways, reducing the production of pro-inflammatory mediators such as iNOS and COX-2. MAPK signaling regulates cellular functions including proliferation, apoptosis, and immune responses, while oxidative stress caused by excessive reactive oxygen species (ROS) further exacerbates inflammation and tissue damage. Furthermore, an excess of reactive oxygen species (ROS) might have a negative impact on the oxidative metabolism of cells or tissues, leading to structural and functional impairment and intensifying inflammatory responses (**Figure 1**).[10]

Macrophage polarization is a key immunomodulatory process in which macrophages differentiate into M1 and M2 types. M1 macrophages promote inflammation and pathogen clearance, whereas M2 macrophages support tissue repair and regulate inflammatory responses.[12] Neutrophils, produced in the bone marrow, are early responders to infection and inflammation, eliminating pathogens and restoring homeostasis. They contain oxidants, proteases, and other cytotoxic substances, making them effective but potentially harmful, contributing to non-infectious diseases.[13] Neutrophils also form neutrophil extracellular traps (NETs), which enhance immune defense but can amplify inflammation. NET formation (NETosis) is associated with inflammatory conditions such as sepsis, diabetes, and rheumatoid arthritis.[14]

The skin, constantly exposed to environmental stressors, is highly susceptible to inflammation. This leads to immune cell infiltration, keratinocyte hyperproliferation, barrier disruption, and extracellular matrix remodeling, contributing to inflammatory skin disorders (**Figure 2**).[15]

Skin inflammatory disorders often begin with epithelial barrier dysfunction, which triggers type 2 immune responses. This conserved immune pathway promotes tissue repair and protects against parasites and toxins. When the barrier is disrupted, cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) recruit eosinophils and basophils while activating mast cells, dendritic cells, and group 2 innate lymphoid cells (ILC2s). These cells coordinate the release of type 2 cytokines, histamine, and other mediators to eliminate harmful agents and restore tissue integrity. However, persistent barrier damage or hypersensitivity can lead to chronic inflammation and disease.[16-18]

Common inflammatory skin disorders include psoriasis, atopic dermatitis, and lupus erythematosus. Psoriasis affects 2–3% of the population and is driven by T-helper 17 (Th17) cells, with key cytokines such as IL-17, IL-22, and IL-23. It is characterized by epidermal hyperproliferation, abnormal differentiation, and red, scaly

plaques.[15] Atopic dermatitis (eczema) involves barrier dysfunction, pruritus, and a Th2-dominant response with elevated IL-4 and IL-13, while chronic stages also involve IFN-γ, IL-17, and IL-22.[19] Systemic sclerosis (scleroderma) differs by causing fibrosis through excessive extracellular matrix deposition, vascular damage, and immune dysregulation, often leading to multi-organ complications.[15]

Systemic inflammation can further complicate these conditions, ranging from stable disease to severe multiorgan failure.[20] It is crucial to address skin inflammation promptly and appropriately in order to prevent the condition from further deteriorating. The preservation of the epidermis barrier is also crucial; it not only influences the efficacy of the disease's treatment but also influences its prognosis. Effective management requires maintaining skin barrier integrity and using treatments such as moisturizers, corticosteroids, immunomodulators, phototherapy, and antihistamines. However, responses vary, and conventional therapies may cause adverse effects. Consequently, interest in safer alternatives has grown, particularly herbal medicine.[21] *Averrhoa bilimbi* Linn leaf has gained attention for its potential anti-inflammatory properties, offering a promising natural approach for managing inflammatory skin conditions.

Efficacy of *Averrhoa bilimbi* Linn Leaf Treatments in inflammation

Averrhoa bilimbi Linn (*Oxalidaceae*) is a tropical plant widely used in traditional medicine for conditions such as asthma, rheumatism, and gastrointestinal disorders (**Figure 3**). Native to Malaysia and cultivated across Southeast Asia, its leaves show antibacterial, anticoagulant, analgesic, and anti-inflammatory properties. Abundant and underutilized, the leaves offer promising therapeutic potential, supported by studies demonstrating moderate anti-inflammatory effects of their methanolic extracts.[22,23]

Scientific Classification:[25]

Kingdom : Plantae – Plants

Subkingdom : Tracheobionta – Vascular plants

Superdivision : Spermatophyta – Seed plants

Division : Magnoliophyta – Flowering plants

Class : Magnoliopsida – Dicotyledons

Subclass : Rosidae

Order : Geraniales

Family : *Oxalidaceae* – Wood-Sorrel family

Genus : *Averrhoa Adans – averrhoa*

Species : *Averrhoa bilimbi* Linn – *bilimbi*.

Averrhoa bilimbi Linn contains diverse phenolic compounds, including tannins, saponins, coumarins, flavonoids, quinones, anthocyanins, and alkaloids, which contribute to its antioxidant, anti-inflammatory, and antibacterial properties.[24,26,27] Flavonoids, anthocyanins, and catechins are particularly effective in neutralizing free radicals due to their ability to donate electrons or hydrogen atoms. Among plant parts, methanolic bark extracts show the highest phenolic content, while fruits have the lowest.[28] Flower extracts also exhibit antioxidant activity, attributed to compounds such as hexanedioic acid, γ-sitosterol, and hexadecanoic acid, supporting their antibacterial and anti-inflammatory potential.[29] Flavonoids possess multiple pharmacological effects, including antioxidant, anticancer, and anti-inflammatory activities. They may also inhibit tyrosinase activity, influenced by structural features such as hydroxyl groups, which disrupt enzyme function.[30]

Antioxidants in *Averrhoa bilimbi* act by reducing reactive oxygen species (ROS), forming metal complexes, and neutralizing reactive metabolites, thereby limiting oxidative stress and inflammation.[31] Additionally, polyphenols may suppress inflammatory responses by inhibiting MHC-II expression on dendritic cells, reducing cytokine production by Th2 cells and IgE synthesis.[32]

Experimental studies further confirm its anti-inflammatory activity. Methanolic extracts of leaves and bark significantly reduced carrageenan-induced paw edema in rats, surpassing diclofenac sodium (10 mg/kg), likely through inhibition of prostaglandin pathways and mediators such as TNF-α.[33] Another study demonstrated that ethanolic leaf extracts, rich in flavonoids and phenolics, effectively stabilized cell membranes and inhibited hemolysis, indicating strong anti-inflammatory effects.[34]

Beyond its anti-inflammatory effects, *Averrhoa bilimbi* Linn leaves exhibit strong antioxidant activity that helps prevent chronic inflammation. A study by Wardoyo et al. showed that leaf extract significantly reduced malondialdehyde (MDA) levels in diabetic mice, indicating decreased oxidative stress, while also prolonging clotting time, suggesting anticoagulant effects. This is important because chronic inflammation is often linked to oxidative stress, hypercoagulability, and endothelial dysfunction. By modulating these pathways, the extract may help prevent diseases such as diabetes, arthritis, and cardiovascular disorders.[35]

Phytochemical analyses reveal that *Averrhoa bilimbi* contains secondary metabolites such as flavonoids, alkaloids, polyphenols, tannins, and terpenes. These compounds demonstrate strong antibacterial activity against pathogens including *Staphylococcus aureus* and *Salmonella typhi*.[36] Leaf constituents like saponins, tannins, and flavonoids inhibit bacterial growth by disrupting enzymes, cell membranes, and protein functions, leading to cell damage and death.[37,38]

Despite promising findings, clinical evidence remains limited. Most studies are in vitro or animal-based, with few large-scale human trials. There is also insufficient data on its effects across different inflammatory skin conditions. Standardized dosing, safety, and long-term

efficacy require further investigation to validate its dermatological applications.

Safety and Toxicity of *Averrhoa bilimbi* Linn Leaf Treatments

Averrhoa bilimbi Linn leaf extract demonstrates notable anti-inflammatory and wound-healing properties, largely attributed to bioactive compounds such as saponins, tannins, and flavonoids. Experimental studies show that a dose of 200 mg/kg body weight significantly enhances incision wound repair in male rodents. These effects are supported by its antibacterial, antioxidant, and anti-inflammatory activities, as well as its ability to increase fibroblast proliferation, a key factor in tissue regeneration. Additionally, topical application of a 2% gel formulation of the leaf extract has been shown to effectively accelerate wound healing in rat models.[39]

Despite these therapeutic benefits, safety and toxicity considerations remain important. *Averrhoa bilimbi* fruit contains high levels of oxalic acid, which has been associated with acute kidney injury and elevated creatinine levels due to calcium oxalate crystal deposition in renal tubules. Excessive consumption may lead to severe nephrotoxicity requiring interventions such as hemodialysis, although mild cases may resolve without specific treatment.[40]

The LD50 (lethal dose 50) values of the 80% ethanol extract of *Averrhoa bilimbi* Linn fruit given orally to female Sprague Dawley Rats were greater than 5,000 mg/kg BW, as determined by the acute and subchronic toxicity experiments. The behavior of the test animal did not change, and no mortality occurred during this experiment. Practically, non-toxic is defined as an LD50 exceeding 5.000 mg/kg in accordance with acute toxicity criteria. In a 28-day brief sub-chronic toxicity assessment, the 80% ethanol extract of *Averrhoa bilimbi* Linn fruit was orally fed to male and female Sprague Dawley rats. The findings demonstrated that there were no fatalities, toxic manifestations, or alterations in body weight at any of the administered doses: 125 mg/kg BW, 250 mg/kg BW, and 500 mg/kg BW. The toxicity assessment of 70% ethanol extract from *Averrhoa bilimbi* Linn leaves on shrimp larvae (*Artemia salina* L.*)* with the brine shrimp lethality test (BSLT) method revealed a moderate toxic effect, with an LC50 (lethal concentration 50) value of 367.28 µg/mL. The ethanol extract of 95% *Averrhoa bilimbi* Linn leaves exhibited LC50 and LC90 values of 5.81 and 10.28 µg/mL, respectively, in shrimp larvae, as determined by the brine shrimp lethality bioassay method.[41]

Importantly, the safety profile of *Averrhoa bilimbi* leaves, particularly for dermatological use, remains insufficiently studied. While toxicity data are more established for the fruit, limited evidence exists regarding the long-term safety of leaf extracts. Potential drug interactions and effects in vulnerable populations, such as children, the elderly, or individuals with underlying conditions, are not well understood. Therefore, further well-designed clinical studies are essential to confirm the safety, efficacy, and optimal use of *Averrhoa bilimbi* Linn leaf as an anti-inflammatory therapeutic agent.

Mechanisms of Action of *Averrhoa bilimbi* Linn Leaf Treatments in inflammation

Averrhoa bilimbi Linn contains diverse phytoconstituents, including alkaloids, glycosides, tannins, steroids, and saponins, contributing to its therapeutic potential. Its fruit extract exhibits strong antioxidant activity through free radical scavenging, supporting its use in cardiovascular, inflammatory, and aging-related conditions, as well as skin care applications.[42] The methanolic leaf extract has demonstrated significant anti-inflammatory effects in carrageenan-induced edema, comparable to ibuprofen, with activity lasting 2–4 hours. It also showed notable analgesic effects (67.51%) at 400 mg/kg, similar to diclofenac sodium.[43]

Despite these promising findings, the mechanisms underlying its anti-inflammatory effects remain insufficiently understood. Limited studies explore its interaction with key inflammatory pathways, including cytokines and mediators such as TNF-α, IL-6, and NF-κB, or its role in oxidative stress modulation. Additionally, data on pharmacokinetics, bioavailability, and skin absorption are lacking. Further mechanistic research is crucial to establish *Averrhoa bilimbi* Linn as a scientifically supported natural anti-inflammatory agent and to determine its precise role in dermatological treatments (**Figure 4**).[43]

Challenges and Limitations in the Use of *Averrhoa bilimbi* Linn Leaf Treatments

The clinical use of *Averrhoa bilimbi* Linn leaf as an anti-inflammatory agent faces key limitations. A major challenge is the lack of standardization in formulation, including variations in extraction methods, dosage forms, and bioactive compound concentrations, leading to inconsistent efficacy and safety. Additionally, the absence of clear clinical guidelines reduces confidence among healthcare professionals. Research is also limited in specific populations, such as children, the elderly, and patients with comorbidities. These gaps hinder its broader application, highlighting the need for rigorous studies and standardized protocols to ensure safe and effective use.

Future Directions and Research Recommendations

Future research on *Averrhoa bilimbi* Linn leaf should prioritize large-scale randomized controlled trials to confirm its efficacy and safety in humans. Standardization of extraction methods, formulations, and dosage is essential to ensure consistent results. Mechanistic studies are also needed to identify active compounds and clarify their roles in inflammatory pathways. Additionally, developing clear clinical guidelines and educational resources will support safe use. These efforts will strengthen the scientific foundation for its application as a natural anti-inflammatory therapy.

4. DISCUSSION

The leaf *Averrhoa bilimbi* Linn shows significant potential as an anti-inflammatory agent, attributed to its abundant

bioactive components such as flavonoids, tannins, and saponins, which possess antioxidant and anti-inflammatory characteristics. Initial research suggests it may assist in controlling skin inflammation by regulating oxidative stress and inflammatory mechanisms. Nonetheless, despite these encouraging results, the clinical data substantiating its effectiveness remains insufficient. The absence of extensive randomized controlled trials, standardized formulations, and thorough safety assessments presents considerable obstacles to its practical implementation.

From a clinical perspective, the current findings suggest that *Averrhoa bilimbi* Linn leaf could serve as an alternative or complementary treatment for inflammatory conditions, particularly in dermatology. Nonetheless, the lack of standardized clinical guidelines and clearly defined safety protocols hinders healthcare providers from confidently incorporating it into conventional therapy alternatives. Mitigating these restrictions is crucial to guarantee its safe and successful application. Additional research is necessary to address these deficiencies. Future research should prioritize the execution of high-quality randomized controlled trials to ascertain its therapeutic efficacy, developing standardized dosage and formulation guidelines, and exploring its precise mechanism of action at a molecular level. Additionally, comprehensive toxicity and safety studies, particularly long-term evaluations and drug interaction assessments, are necessary to confirm its suitability for widespread medical use. Strengthening scientific evidence through these research efforts will not only validate the therapeutic potential of *Averrhoa bilimbi* Linn leaf but also facilitate its incorporation into evidence-based anti-inflammatory treatments, ensuring both efficacy and patient safety.

Conflict of Interest
The authors declare no conflict of interest.

Author's Declaration
The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

ACKNOWLEDGEMENT
Not applicable.

REFERENCES

1. Stone WL, Basit H, Zubair M, et al. Pathology, Inflammation. [Updated 2024 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534820/
2. Roe K. An inflammation classification system using cytokine parameters. Scand J Immunol. 2021;93(2):e12970.
3. Panigrahy D, Gilligan MM, Serhan CN, Kashfi K. Resolution of inflammation: An organizing principle in biology and medicine. Pharmacol Ther. 2021;227:107879.
4. Saggar S, Mir PA, Kumar N, Chawla A, Uppal J, Kaur A. Traditional and herbal medicines: opportunities and challenges. Pharmacognosy Research. 2022;14(2):107.
5. Cruz-Martins N. Molecular Mechanisms of Anti-Inflammatory Phytochemicals 2.0. Int J Mol Sci. 2023;24(24):17443.
6. Guo M, Qin S, Wang S, Sun M, Yang H, Wang X, Fan P, Jin Z. Herbal Medicine Nanocrystals: A Potential Novel Therapeutic Strategy. Molecules. 2023;28(17):6370.
7. Yang Y, Xiao G, Cheng P, Zeng J, Liu Y. Protective Application of Chinese Herbal Compounds and Formulae in Intestinal Inflammation in Humans and Animals. Molecules. 2023;28(19):6811.
8. Kang KS. Phytochemical Constituents of Medicinal Plants for the Treatment of Chronic Inflammation. Biomolecules. 2021;11(5):672.
9. Setyawan HY, Sukardi S, Nareswari BF. The phytochemical potential of *Averrhoa bilimbi*–A review. In IOP Conference Series: Earth and Environmental Science. 2021:733(1):012091.
10. Liu H, Zhang L, Yu J, Shao S. Advances in the application and mechanism of bioactive peptides in the treatment of inflammation. Front Immunol. 2024;15:1413179.
11. Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. CNS Neurosci Ther. 2021;27(1):36-47.
12. Martins RA, Costa FR, Pires L, Santos M, Santos GS, Lana JV, Costa BR, Santos N, de Macedo AP, Kruel A, Lana JF. Regenerative Inflammation: The Mechanism Explained from the Perspective of Buffy-Coat Protagonism and Macrophage Polarization. Int J Mol Sci. 2024;25(20):11329.
13. Singhal A, Kumar S. Neutrophil and remnant clearance in immunity and inflammation. Immunology. 2022;165(1):22-43.
14. Li X, Xiao S, Filipczak N, Yalamarty SSK, Shang H, Zhang J, Zheng Q. Role and Therapeutic Targeting Strategies of Neutrophil Extracellular Traps in Inflammation. Int J Nanomedicine. 2023;18:5265-5287.
15. Shutova MS, Boehncke WH. Mechanotransduction in Skin Inflammation. Cells. 2022;11(13):2026.
16. Kim B, Rothenberg ME, Sun X, Bachert C, Artis D, Zaheer R, Deniz Y, Rowe P, Cyr S. Neuroimmune interplay during type 2 inflammation: Symptoms, mechanisms, and therapeutic targets in atopic diseases. J Allergy Clin Immunol. 2024;153(4):879-893.

17. Kim BE, Kim J, Goleva E, Berdyshev E, Lee J, Vang KA, Lee UH, Han S, Leung S, Hall CF, Kim NR, Bronova I, Lee EJ, Yang HR, Leung DY, Ahn K. Particulate matter causes skin barrier dysfunction. JCI Insight. 2021;6(5):e145185.

18. Yang G, Seok JK, Kang HC, Cho YY, Lee HS, Lee JY. Skin Barrier Abnormalities and Immune Dysfunction in Atopic Dermatitis. Int J Mol Sci. 2020;21(8):2867.

19. Li Y, Li L. Contact Dermatitis: Classifications and Management. Clin Rev Allergy Immunol. 2021;61(3):245-281.

20. Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, Fernández J, Gustot T, Caraceni P, Bernardi M; investigators from the EASL-CLIF Consortium, Grifols Chair and European Foundation for the Study of Chronic Liver Failure (EF-Clif). The systemic inflammation hypothesis: Towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol. 2021;74(3):670-685.

21. Kulthanan K, Tuchinda P, Nitiyarom R, Chunharas A, Chantaphakul H, Aunhachoke K, Chularojanamontri L, Rajatanavin N, Jirapongsananuruk O, Vichyanond P, Chatchatee P, Sangsupawanich P, Wananukul S, Singalavanija S, Trakanwittayarak S, Rerkpattanapipat T, Thongngarm T, Wisuthsarewong W, Limpongsanurak W, Kamchaisatian W, Noppakun N. Clinical practice guidelines for the diagnosis and management of atopic dermatitis. Asian Pac J Allergy Immunol. 2021;39(3):145-155.

22. Hari N, Priya C, Besteena E, Kavya V. A COMPARATIVE MORPHO-ANATOMICAL STUDY OF LEAF AND STEM IN *AVERRHOA BILIMBI* L. AND *AVERRHOA CARAMBOLA* L. L.-Life Sciences International Research Journal. 2020;7(1):54-60.

23. Widiastuti D, Sinaga SE, Warnasih S, Pujiyawati E, Salam S, Putra WE. "Identification of Active Compounds from *Averrhoa bilimbi* L. (Belimbing Wuluh) Flower using LC-MS and Antidiabetic Activity Test using in vitro and in silico Approaches", Trends in Sciences. Nakhon Si Thammarat, Thailand. 2023;20(8):6761.

24. Arifin RNAR, Jumal J. Antioxidant activity of *Averrhoa bilimbi* Linn. leaves extract using two different types of solvents. Malaysian Journal of Science Health & Technology. 2020;7:1.

25. Birla DK, Patel R. ASSESSMENT OF PHYTOCHEMICAL INVESTIGATION AND ANTIMUTAGENIC ACTIVITY OF *AVERRHOA BILIMBI*. 2019;9(6):1131-1136.

26. Iwansyah AC, Desnilasari D, Agustina W, Pramesti D, Indriati A, Mayasti NKI, Kormin FB. Evaluation on the physicochemical properties and mineral contents of *Averrhoa bilimbi* L. leaves dried extract and its antioxidant and antibacterial capacities. Food Science and Technology. 2021;41:987-992.

27. Sarker MAM, Chowdhury AYSFUA. "Analgesic effect of methanolic extracts of leaf, bark and fruit of *Averrhoa bilimbi* Linn: Analgesic effect of methanolic extracts", Bangladesh Medical Research Council Bulletin. 2023;48(2):120–126.

28. Sarker MAM, Chowdhury AYSFUA. "Estimation of Total Phenolic Content and Antioxidant Activity of Methanolic Extracts of Leaf, Bark and Fruit of *Averrhoa bilimbi* Linn: Phenolic Content and Antioxidant Activity of Methanolic Extracts of *Averrhoa bilimbi* Linn", Bangladesh Medical Research Council Bulletin. 2024;50(1):10–14.

29. Wibawa IPAH, Sutomo, Lugrayasa IN. "Antioxidant assay of *Averrhoa bilimbi* L flower extract, chemical compound and its utilization potential". Berkala Penelitian Hayati. 2022:28(1):72-77.

30. Thummajitsakul S, Silprasit K. "Kinetics of Tyrosinase Inhibition, Antioxidant Activity, Total Flavonoid Content and Analysis of *Averrhoa bilimbi* L. Extracts and its Fruit Vinegar Using FTIR and Multivariate Methods", Trends in Sciences. Nakhon Si Thammarat. 2022;20(2):3641.

31. Bakyalakshmi G, Rsridhar R. COMPARATIVE ANALYSIS OF THE PHYTOCHEMICALS, ANTIOXIDANT AND ANTICANCER POTENTIAL OF LEAVES OF *AVERRHOA BILIMBI* LINN AND *QUISQUALIS INDICA* L. 2023;8(1).

32. Santoso WH, Ishida M, Nishi K, Sugahara T, Putra ABN. "Anti-Allergy Potential of *Averrhoa bilimbi* Linn. Fruit Water Extract Shown by Its Suppressive Effect on the Degranulation of RBL-2H3 Cells". Journal of Functional Food and Nutraceutical. 2021;2(2):81-88.

33. Sarker MAM, Chowdhury AYSFUA. Acute anti-inflammatory effect of methanolic extracts of leaf, bark and fruit of Averrhoa bilimbi on carrageenan-induced acute inflammation in rats. J Pharmacogn Phytochem. 2024;13(5):97-101

34. Hasim H. Ekstrak Etanol Daun Belimbing Wuluh (Averrhoa bilimbi) sebagai Antioksidan dan Antiinflamasi. J Apl Teknol Pangan. 2021;10(2):123-130.

35. Wardoyo RAG, Qomariyah N, Purnama ER. Effect of Averrhoa bilimbi Leaf Extract on Malondialdehyde Levels and Clotting Time of Diabetic Mice. LenteraBio. 2023;12(1):1-8.

36. Anindita R, Nathalia DD, Perwitasari M, Putri IK, Beandrade MU, Harahap NRA. Antibacterial Bioactivity Test of Bilimbi Fruit Ethanol Extract

(*Averrhoa bilimbi* Linn). Against Propionibacterium acnes, Staphylococcus epidermidis and Staphylococcus aureus. Biology, Medicine, & Natural Product Chemistry. 2-24;13(1):173-182.

37. Widiatami T, Rasipin R, Fatmasari D. EFFECTIVENESS EFFECTIVENESS OF THE GIVING STARFRUIT LEAF EXTRACT (*AVERRHOA BILIMBI* L.) AND CINNAMON (*C. BURMANII*) AS AN ALTERNATIVE TO ANTIBACTERIALS FOR THE HEALING OF PERINEUM WOUNDS IN RATTUS NORVEGICUS. INTERNATIONAL JOURNAL OF NURSING AND MIDWIFERY SCIENCE (IJNMS). 2022;5(3):176-184.
38. Zarwinda I, Fauziah F, Jumirna J, Adriani A. The Formulation Of Peel-Off Mask From The Ethanol Extract Of Bilimbi Leaves (*Averrhoa Bilimbi* L.) As Anti-Acne Treatment. Lantanida Journal. 2021;9(1):499035.
39. Suena NMDS, Nayaka NMDMW, Wardani IGAAK, Antari NPU. "Bilimbi (*Averrhoa bilimbi* L.) Leaf Extract Cream: Formulation and Efficacy in Accelerating Wound Healing in Male White Mice". Jurnal Kefarmasian Indonesia. 2024;1:223–235.
40. Prasad, Sruthy C, Velayudhan K, Reghu R. "Consumption of bilimbi cause acute kidney injury." International Journal of Research in Pharmaceutical Sciences. 2021;12:653-655.
41. Leliqia NPE, Safitri I. A Review of Phytochemical Properties, Antibacterial Activity, And Toxicity Study of *Averrhoa bilimbi* Leaves And Fruit. Journal of Pharmaceutical Science and Application. 2021;3(1):32.
42. Nathania M, Wasito EB, Hasanathuludhiyah N. In Vitro Antibacterial Activity of *Averrhoa bilimbi* Leaves Ethanol Extract against *Salmonella typhi*. JUXTA J Ilm Mhs Kedokt Univ Airlangga. 2021;14:42-45.
43. Garg M, Chaudhary SK, Kumari S, Goyal A. Phytochemical, Biological and Traditional Claims on *Averrhoa bilimbi*: An Overview. Indian Journal of Pharmaceutical Sciences. 2022: 84(3).

Multimedia Appendices

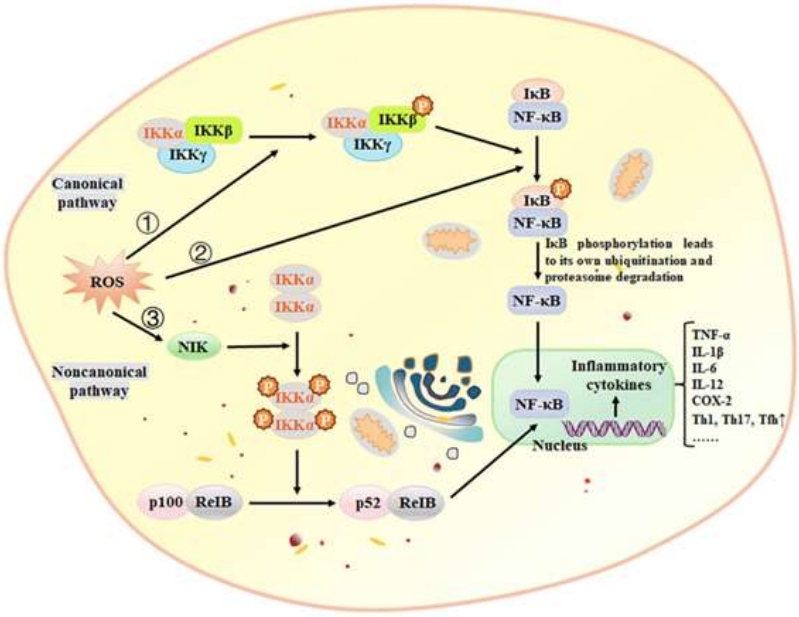

Figure 1. ROS activate NF-kB through three pathways.[10]

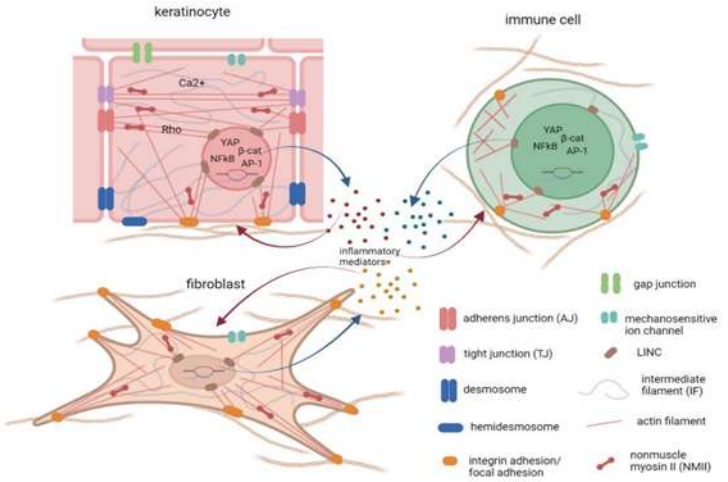

Figure 2. Skin inflammation mechanism.[15]

Figure 3. *Averrhoa bilimbi* Linn leaves and fruits.[24]

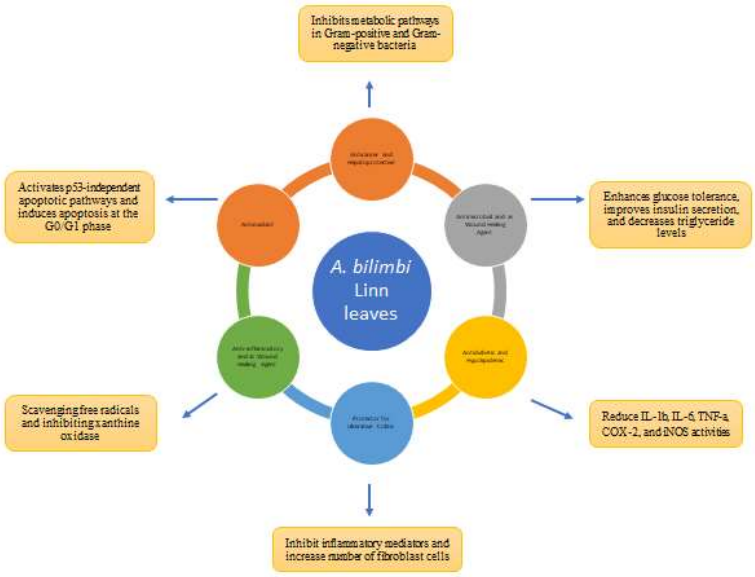

Figure 4. Potential role of *Averrhoa bilimbi* Linn.[43]