



In silico evaluation of neem phytochemicals as modulators of pro-inflammatory cytokines: potential host directed adjuncts for lymphatic filariasis

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Abstract

Lymphatic filariasis (LF) is a neglected tropical disease that causes chronic morbidity through lymphatic dysfunction, fibrosis, and immune dysregulation. Pro-inflammatory cytokines and chemokines, including TNF- α , IL-6, IL-1 β , MIP-1 α , and MIP-1 β , are central to LF pathology by amplifying inflammation and promoting tissue remodeling. While mass drug administration (MDA) effectively targets parasites, it does not reverse established pathology, showing the need for host-directed therapies. Neem (*Azadirachta indica*) contains phytochemicals with immunomodulatory potential. In this study, molecular docking was performed to evaluate the interactions of nimbolide, azadirachtin, and nimbin with key inflammatory mediators. Nimbolide consistently exhibited the strongest binding affinities to IL 6R (−7.8 kcal/mol), IL 16 (−7.5 kcal/mol), and TNF α (−7.5 kcal/mol). Azadirachtin showed selective high affinity for TNF- α (−7.1 kcal/mol), while nimbin demonstrated moderate, broad-spectrum interactions (−5.7 to −6.8 kcal/mol). LigPlot+ analysis confirmed stable hydrogen bonding and hydrophobic contacts, especially for nimbolide. Pharmacokinetic predictions using the BOILED-Egg model indicated favorable gastrointestinal absorption for nimbolide and nimbin, with poor blood-brain barrier penetration, suggesting systemic efficacy with minimal CNS exposure. Azadirachtin, however, showed poor compliance with drug-likeness and absorption criteria. Neem phytochemicals, especially nimbolide and azadirachtin, may reduce cytokine-driven inflammation, lymphatic dysfunction, and fibrosis. Although preliminary and computational, the results provide a rational basis for further validation, as well as pharmacokinetic and safety studies. Neem-derived compounds could act as adjuncts to MDA and improve LF morbidity management in endemic regions.

Keywords Lymphatic filariasis · *Azadirachta indica* · Nimbolide · Azadirachtin · Nimbin · Cytokine modulation · Host-directed therapy · Molecular docking · BOILED-Egg model · Neglected tropical disease

Introduction

Lymphatic filariasis (LF) is a mosquito-borne parasitic disease caused primarily by *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori* (Al-Tameemi and Kabakli 2019). It remains one of the leading causes of chronic disability worldwide and is classified by the World Health Organization (WHO) as a major neglected tropical disease. Despite decades of control programs, LF is still endemic in 39 countries, with over 650 million people requiring preventive chemotherapy and an estimated 40 million suffering from chronic complications such as lymphedema, hydrocele, and elephantiasis (WHO 2023; Joshi 2018). Beyond physical deformities, the disease carries profound psychosocial and

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economic burdens, particularly in low-resource endemic regions (Joardar et al. 2021).

Since LF is transmitted through mosquito vectors such as *Culex*, *Anopheles*, and *Aedes*, vector management remains an important component of disease control programmes aimed at reducing transmission intensity. Plant-derived interventions, including neem-based formulations, have demonstrated larvicidal and repellent activity against mosquito species, supporting their role within integrated filariasis management strategies (Chatterjee et al. 2023, 2024; Bag et al. 2022a, b, 2025a, b; Adhikary et al. 2024; Bag and Chatterjee 2025; Saha et al. 2025). However, the present study primarily focuses on the host-directed immunomodulatory potential of neem phytochemicals in regulating cytokine-mediated inflammatory pathology associated with lymphatic filariasis.

The pathology of LF is not solely a consequence of parasite presence but also of immune dysregulation. Adult worms residing in lymphatic vessels trigger immune activation, endothelial damage, and lymphatic dilation, while circulating microfilariae interact with innate and adaptive immune cells. Dysregulated pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β), along with chemokines such as Macrophage Inflammatory Protein-1 α (MIP-1 α) and Macrophage Inflammatory Protein-1 β (MIP-1 β), amplify inflammatory cascades, promote pathological lymphangiogenesis via vascular endothelial growth factor (VEGF), and drive tissue fibrosis (Chakraborty et al. 2013; Babu and Nutman 2014). Elevated cytokine and chemokine levels have been linked to more severe chronic pathology compared to asymptomatic carriers, underscoring their central role in LF progression (Bennuru et al. 2018). Consequently, modulation of these mediators has been proposed as a host-directed therapeutic strategy to reduce tissue damage and morbidity (Nisar et al. 2023), complementing existing antifilarial drugs that primarily target parasites.

Among natural sources of immunomodulators, neem (*Azadirachta indica*) holds particular significance. Revered in traditional medicine as a “village pharmacy,” neem possesses diverse pharmacological properties, including antimicrobial, antioxidant, antifilarial, anticancer, and anti-inflammatory activities (Islas et al. 2020; Sarkar et al. 2021; Wylie and Merrell 2022). Its phytochemicals especially limonoids such as nimbolide, azadirachtin, and nimbin have demonstrated the ability to suppress NF- κ B activation, inhibit MAPK signaling, reduce cytokine secretion, and mitigate oxidative stress (Sarkar et al. 2021; Wylie and Merrell 2022). These properties make neem-derived compounds attractive candidates for modulating immune responses in chronic inflammatory diseases such as LF.

Recent advances in computational methods, particularly molecular docking, enable efficient screening of natural products against specific protein targets. Docking can predict binding affinities and interaction modes of phytochemicals with cytokines and receptors, allowing rapid identification of promising modulators prior to experimental validation (Trott and Olson 2009). In parallel, predictive pharmacokinetic models such as the BOILED-Egg provide insights into absorption and blood–brain barrier (BBB) permeability (Daina and Zoete 2016). Notably, nimbolide and nimbin are predicted to exhibit favourable gastrointestinal absorption but poor BBB penetration, suggesting systemic efficacy with minimal central nervous system side effects—a desirable trait for LF therapy. Conversely, azadirachtin shows poor oral bioavailability, limiting its translational potential despite selective cytokine binding affinity. Taken together, these insights suggest that neem phytochemicals could serve as host-directed adjunct therapies in LF by targeting cytokine-driven inflammation and fibrosis. This study employs in silico docking and pharmacokinetic prediction to evaluate nimbolide, azadirachtin, and nimbin against TNF- α , IL-6R, IL-1 β , MIP-1 α , and MIP-1 β , thereby providing a foundation for future experimental validation. Integrating immunomodulatory phytochemicals with antifilarial regimens may help alleviate morbidity and contribute to sustainable, affordable management strategies for LF in endemic regions (WHO 2020).

Pathophysiology and immunology of lymphatic filariasis

Lymphatic filariasis is caused by parasitic nematodes *W. bancrofti*, *B. malayi* and *B. timori* that specifically target the human lymphatic system. The life cycle of these parasites involves both human and mosquito hosts. Infective larvae (L₃) are transmitted to humans through mosquito bites, where they migrate to lymphatic vessels and mature into adult worms over 6–12 months. Adult worms reside primarily in lymphatic vessels and lymph nodes, producing microfilariae that circulate in peripheral blood, which can then be taken up by mosquitoes during subsequent blood meals (WHO 2023). This lymphatic tropism is central to disease pathology, as adult worms obstruct lymphatic flow and trigger immune-mediated tissue damage. The host immune response to filarial infection involves a complex interplay between innate and adaptive immunity. Initially, innate immune cells including macrophages, dendritic cells and neutrophils recognize filarial antigens via pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). This triggers the production of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and chemokines (MIP-1 α , MIP-1 β),

which recruit additional immune cells to the infection site (Babu and Nutman 2014). Adaptive immunity develops with the activation of Type 1 T helper cell (Th1), Type 2 T helper cell (Th2) and Th17 lymphocyte subsets, producing cytokines that can both control parasite load and contribute to lymphatic inflammation. In asymptomatic carriers, a balance between regulatory T cells and effector responses allows parasite persistence without severe pathology, whereas in patients with chronic disease, dysregulated immune responses lead to tissue damage (Chakraborty et al. 2013).

The cytokine and chemokine networks play a pivotal role in the development of lymphatic inflammation. Persistent activation of TNF- α , IL-1 β , and IL-6 promotes endothelial cell activation, lymphangiogenesis via VEGF-C, and recruitment of inflammatory leukocytes. Chemokines such as MIP-1 α and MIP-1 β amplify leukocyte infiltration, sustaining chronic inflammation and contributing to lymphatic obstruction. Excessive or prolonged cytokine signaling leads to fibrosis, lymphatic dilation, and impaired lymph flow, which are hallmark features of advanced LF (Chakraborty et al. 2013; Babu and Nutman 2014).

Chronic manifestations of LF, including lymphoedema, elephantiasis and hydrocele, arise from prolonged inflammation and lymphatic dysfunction. Lymphoedema occurs due to lymphatic obstruction and tissue fluid accumulation, while elephantiasis represents severe hypertrophy and fibrosis of affected limbs, leading to disfigurement and disability. Hydrocele, primarily seen in men, results from lymphatic dysfunction in the scrotal region. These complications not only cause physical disability but also psychological and social challenges for affected individuals, particularly in endemic areas where stigma and reduced productivity exacerbate the disease burden (Joardar et al. 2021). Understanding the interplay between parasite biology and host immune responses is essential for developing host-directed therapies. Targeting key cytokines and chemokines that drive lymphatic inflammation offers a promising strategy to reduce tissue damage and improve clinical outcomes. By combining immunological insights with computational approaches, such as molecular docking of bioactive compounds, it is possible to identify natural modulators that may alleviate inflammatory pathology in LF.

Pro-inflammatory cytokines and chemokines as therapeutic targets

The progression and pathology of LF are heavily influenced by host immune responses, particularly pro-inflammatory cytokines and chemokines. These molecules act as key mediators of inflammation, lymphatic endothelial

dysfunction, and tissue remodelling, making them attractive therapeutic targets for host-directed interventions (Fig. 1).

Cytokines

Tumor necrosis factor-alpha (TNF- α) is a pleiotropic cytokine produced primarily by macrophages, dendritic cells, and T lymphocytes in response to filarial antigens. Structurally, TNF- α is a homotrimeric protein that binds to TNFR1 and TNFR2, triggering downstream NF- κ B and MAPK signaling pathways. These pathways mediate inflammation, apoptosis, and lymphangiogenesis, contributing to lymphatic vessel dilation and fibrosis in chronic LF (Babu and Nutman 2014). IL-6 is a multifunctional cytokine produced by immune cells, endothelial cells, and fibroblasts. IL-6 signals via its receptor (IL-6R) and the gp130 co-receptor, activating JAK/STAT3 pathways. In LF, elevated IL-6 levels correlate with increased lymphatic endothelial activation and VEGF-C production, driving pathological lymphangiogenesis and oedema formation (Fig. 1) (Chakraborty et al. 2013). IL-1 β is synthesized as an inactive pro-form by macrophages and requires inflammasome-mediated cleavage for activation. IL-1 β promotes endothelial permeability, leukocyte recruitment, and chronic inflammation, exacerbating lymphatic damage and tissue fibrosis in filarial pathology (Pyrillou et al. 2020). Collectively, TNF- α , IL-6, and IL-1 β orchestrate the inflammatory milieu in LF, and their dysregulated expression is directly linked to chronic complications such as lymphedema, elephantiasis, and hydrocele.

Chemokines

Macrophage Inflammatory Protein-1 α (MIP-1 α /CCL3) and Macrophage Inflammatory Protein-1 β (MIP-1 β /CCL4) are chemokines that recruit monocytes, macrophages, and lymphocytes to sites of infection. In LF, elevated MIP-1 α and MIP-1 β levels facilitate sustained leukocyte infiltration into lymphatic vessels, promoting persistent inflammation and tissue remodeling. These chemokines interact with CCR1, CCR4 and CCR5 receptors on immune cells, amplifying inflammatory signaling and contributing to lymphatic obstruction (Fig. 1) (Babu and Nutman 2014).

Phytochemicals from *A. indica*

Azadirachta indica, commonly referred to as neem, is a fast-growing evergreen tree native to the Indian subcontinent and widely utilized in tropical and subtropical regions. It has been a cornerstone of traditional medicine systems, including Ayurveda, Unani, and Siddha. Neem has been used to treat infections, inflammation, metabolic diseases,

Fig. 1 Inflammatory signaling pathways involve the key cytokines and immune mediators—TNF- α , IL-1 β , IL-6, and chemokines MIP-1 α (CCL3) and MIP-1 β (CCL4)—released from innate immune cells following recognition of filarial antigens. These mediators bind to their respective receptors (TNFR1/TNFR2, IL-6R/gp130, IL-1R1, and CCR1/CCR5), triggering intracellular signaling cascades including NF- κ B, MAPK, and JAK/STAT3 pathways. Activation of these pathways promotes transcription of inflammatory mediators and VEGF-C expression, leading to endothelial activation, leukocyte recruitment, pathological lymphangiogenesis, and chronic lymphatic inflammation. The interplay between innate and adaptive immune responses contributes to lymphatic dysfunction and disease progression

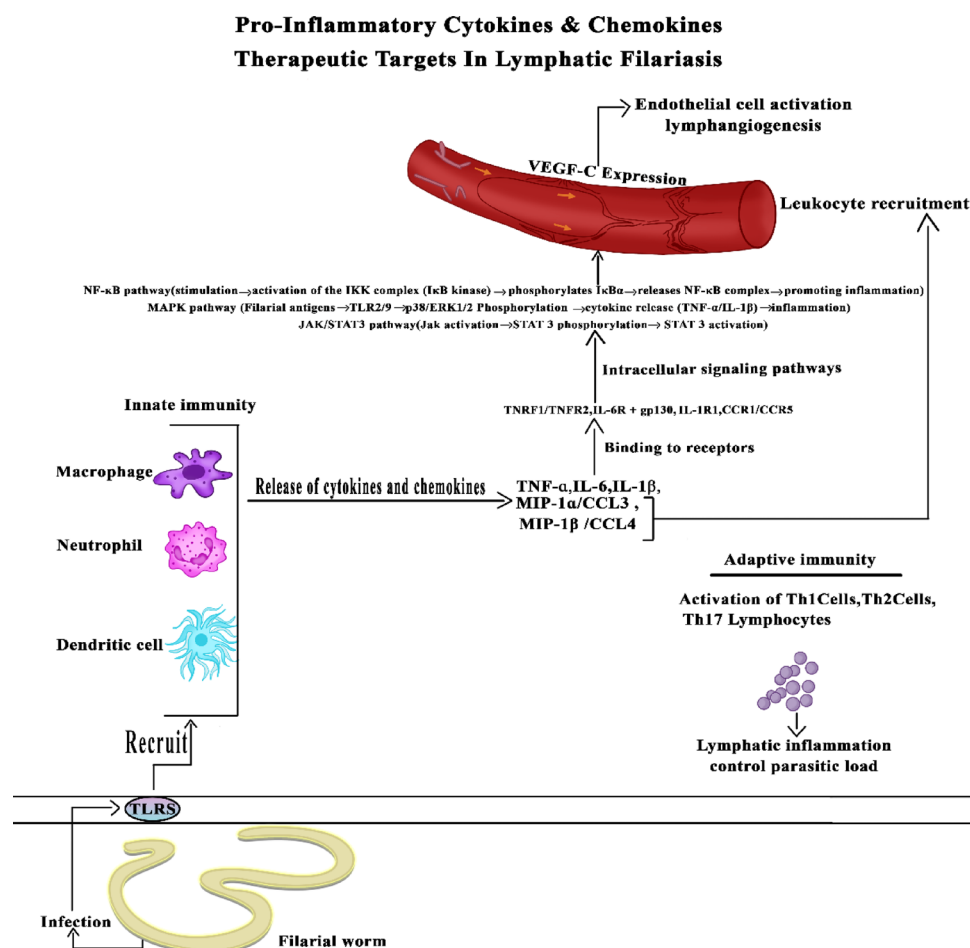


Table 1 SwissADME-based physicochemical and drug-likeness characterization of neem phytochemicals (nimbolide, azadirachtin, and nimbin)

Molecule	Molecular weight (g/mol)	Topological polar surface area ($\text{\AA}^2$)	Consensus Log P (lipophilicity)	Lipinski rule violations	Bioavailability score	Synthetic accessibility (complexity)
Nimbolide	466.52	92.04	3.04	0	0.55	6.07
Azadirachtin	720.71	215.34	1.08	2	0.17	8.11
Nimbin	540.60	118.34	3.24	1	0.55	6.54

and parasitic infestations. Its pharmacological versatility stems from the diverse chemical constituents found in different parts of the plant, including leaves, seeds, bark, and oil, which exhibit antimicrobial, antifilarial, antioxidant, anticancer, antimalarial, and anti-inflammatory activities (Islas et al. 2020).

Physicochemical and drug-likeness profiling

The SwissADME-based physicochemical and drug-likeness profiling highlights the oral bioavailability potential of neem phytochemicals. Nimbolide, with its optimal molecular weight (466.52 g/mol), moderate TPSA (92.04 $\text{\AA}^2$), and balanced lipophilicity (Log P =3.04), meets Lipinski's rule and demonstrates a favorable bioavailability score (0.55),

suggesting good membrane permeability and drug-likeness. Similarly, nimbin, though slightly heavier (540.60 g/mol) with a TPSA of 118.34 $\text{\AA}^2$ and one Lipinski violation, retains a comparable bioavailability score (0.55) and suitable lipophilicity (Log P =3.24), indicating moderate absorption potential. By contrast, azadirachtin shows poor drug-likeness with drug-likeness parameters due to its high molecular weight (720.71 g/mol), excessive TPSA (215.34 $\text{\AA}^2$), two Lipinski violations, and a low bioavailability score (0.17), pointing to limited oral absorption and systemic availability. While nimbolide and nimbin emerge as promising oral drug-like candidates, azadirachtin's structural complexity and poor pharmacokinetic profile suggest it may be more suitable for topical, nanoparticle-assisted, or alternative delivery strategies (Table 1) (Lipinski 2004).

Chemical similarity network

In addition to physicochemical profiling, chemical similarity network analysis was performed to visualize the structural relatedness of the neem phytochemicals with other known bioactive or pesticidal molecules. Each neem compound (nimbolide, azadirachtin, nimbin) was placed at the center of a similarity network, connected to structurally related compounds such as allethrin, pyrethrin I, prallethrin, and spiromesifen, with Tanimoto similarity coefficients indicated along the connecting edges. This comparative mapping highlights shared pharmacophoric features, suggesting that neem-derived limonoids may possess overlapping biological activities with established insecticidal and bioactive scaffolds (Fig. 2).

Immunomodulatory potential

Among the numerous phytochemicals identified in neem, limonoids such as azadirachtin, nimbolide, and nimbin have shown notable promise for modulating immune responses. Azadirachtin, predominantly derived from neem seeds, is widely recognized for its pesticidal effects but has also demonstrated the capacity to regulate inflammatory signalling by inhibiting NF- κ B pathways and reducing the expression of key pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β (Nagini et al. 2024). Nimbolide, a limonoid abundant in neem leaves, exhibits potent anti-inflammatory and antioxidant properties, attenuating oxidative stress and suppressing cytokine release through modulation of NF- κ B and MAPK pathways (Rajendran et al. 2024). Nimbin, although comparatively less studied, has shown preliminary anti-inflammatory effects, highlighting its potential as a novel immunomodulatory agent in disease contexts marked by

chronic inflammation, such as lymphatic filariasis (Sudhakaran et al. 2022).

Pharmacokinetic predictions (BOILED-Egg Model)

The BOILED-Egg model prediction indicates that both nimbolide (blue) and nimbin (red) are positioned inside the white elliptical region, which represents molecules with a high probability of passive gastrointestinal (GI) absorption. BOILED-Egg analysis was performed using the freely accessible SwissADME web tool developed by the Swiss Institute of Bioinformatics (<https://www.swissadme.ch/>). This suggests that both compounds are likely to be well absorbed when administered orally. However, neither compound is located within the yellow yolk region, which marks compounds with a high chance of penetrating the blood–brain barrier (BBB). Therefore, nimbolide and nimbin are predicted to remain largely restricted to systemic circulation without significant entry into the central nervous system. They are suitable for therapies needing GI absorption but not BBB penetration, reducing CNS side effects. In contrast, azadirachtin is positioned outside the BOILED-Egg domain, primarily due to its high polarity and larger molecular size, indicating a low probability of passive GI absorption and negligible BBB permeability. These findings collectively highlight distinct differences in the predicted absorption and distribution profiles of the studied neem-derived bioactive compounds (Fig. 3).

Therapeutic implications

Neem compounds can interfere with cytokine- and chemokine-mediated inflammation. This suggests a promising role for azadirachtin, nimbolide, and nimbinene as candidate molecules for in silico screening and molecular

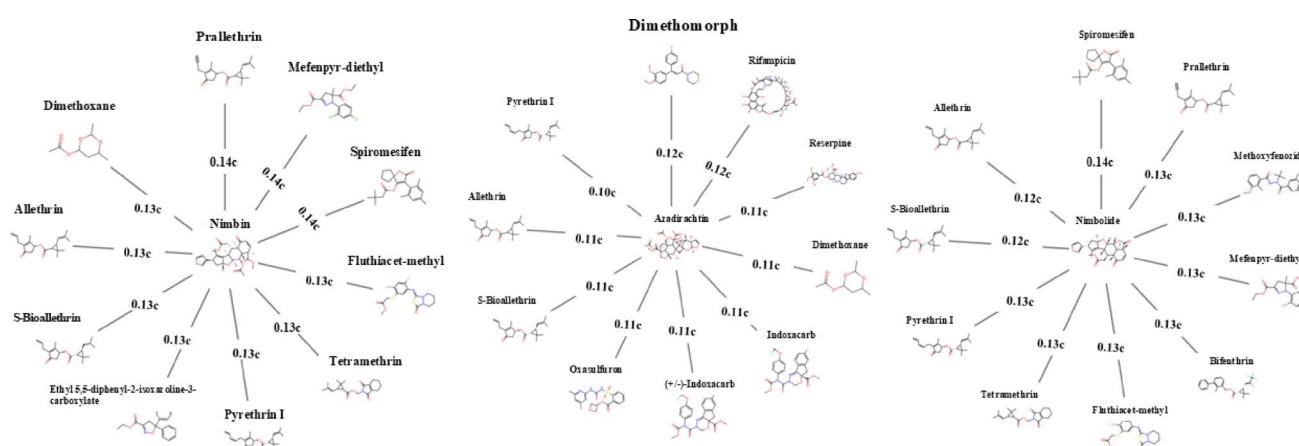


Fig. 2 Chemical similarity network of neem-derived phytochemicals (azadirachtin, nimbolide, and nimbin) constructed using Morgan fingerprints. Central nodes represent neem compounds, connected to

structurally similar bioactive or pesticidal molecules (e.g., allethrin, prallethrin, pyrethrin I, spiromesifen), with edge labels indicating Tanimoto similarity coefficients

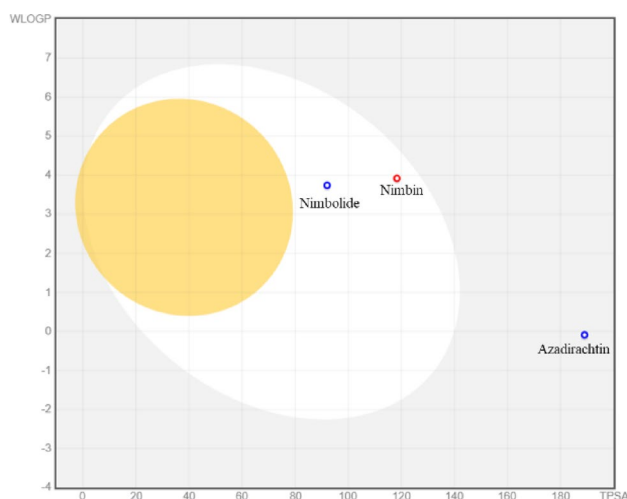


Fig. 3 BOILED-Egg model predicting gastrointestinal (GI) absorption and blood–brain barrier (BBB) permeability of neem phytochemicals. The white region represents a high probability of passive GI absorption, while the yellow region indicates likely BBB permeation. Nimbolide and nimbin are located within the white region but outside the yolk, indicating good GI absorption with poor BBB penetration. In contrast, azadirachtin lies outside the BOILED-Egg domain, suggesting poor GI absorption and negligible BBB permeability due to its high polarity and molecular size

docking studies against inflammatory mediators such as TNF- α , IL-6R, IL-1 β , MIP-1 α , and MIP-1 β . Exploring these interactions may provide insights into their potential as host-directed therapeutic agents capable of mitigating immune-driven pathology in lymphatic filariasis.

Molecular docking of neem phytochemicals against pro-inflammatory cytokines and chemokines

Molecular docking is a computational method that predicts the preferred binding orientation of a ligand to a protein, estimating interaction patterns and binding affinity (Sarkar et al. 2026). It is widely used in drug discovery to identify potential modulators when experimental studies are time-consuming or costly. In LF, docking can evaluate neem phytochemicals azadirachtin, nimbolide and nimbinene against pro-inflammatory cytokines and chemokines involved in disease pathology. The selected targets, TNF- α , IL-6R, IL-1 β , MIP-1 α , and MIP-1 β .

Protein preparation

The binding affinity of neem-derived phytochemicals azadirachtin, nimbolide, and nimbin against pro-inflammatory cytokines and chemokines was assessed through in silico molecular docking analysis utilizing AutoDock Vina v1.1.2 (Eberhardt et al. 2021; Trott and Olson 2009).

The three-dimensional crystal structures of the selected pro-inflammatory cytokines and receptor proteins were retrieved from the Protein Data Bank (PDB) for molecular docking analysis. The structures used included MIP-1 α (PDB ID: 1B50; resolution 2.50 Å), MIP-1 β (PDB ID: 1JE4; resolution 2.10 Å), IL-1 β (PDB ID: 1I1B; resolution 2.20 Å), IL-6 receptor (PDB ID: 1N26; resolution 1.90 Å), and TNF- α (PDB ID: 1TNF; resolution 1.80 Å).

Prior to docking, all protein structures were pre-processed by removing crystallographic water molecules, native ligands, and heteroatoms, followed by the addition of polar hydrogens and Kollman charges using AutoDock Tools v1.5.7 (Trott and Olson 2009). Grid box parameters were defined individually for each target protein based on the predicted ligand-binding regions to ensure adequate conformational sampling during docking simulations. For MIP-1 α (PDB ID: 1B50), the grid box was centered at (x=49.969, y=−0.02, z=−0.015) with dimensions of 60 Å × 44 Å × 52 Å. Docking against IL-1 β (PDB ID: 1I1B) was performed using a grid centered at (x=42.562, y=−14.953, z=23.889) with box dimensions of 48.18 Å × 37.64 Å × 45.17 Å. For MIP-1 β (PDB ID: 1JE4), the grid box center was set at (x=0.33, y=6.183, z=2.752) with dimensions of 27.22 Å × 61.25 Å × 38.11 Å. Docking simulations for IL-6R (PDB ID: 1N26) employed a grid centered at (x=29.226, y=50.808, z=73.061) with dimensions of 76 Å × 68 Å × 98 Å. Similarly, for TNF- α (PDB ID: 1TNF), the grid box was centered at (x=32.455, y=49.675, z=39.93) with dimensions of 94 Å × 88 Å × 58 Å.

Ligand preparation

The phytochemical ligands azadirachtin (CID: 5281303), nimbin (CID: 108058), and nimbolide (CID: 12313376) were obtained from the PubChem database (<http://pubchem.ncbi.nlm.nih.gov/>) in SDF file format. The SDF files were converted to PDB format using the Open Babel module in Avogadro2 software. Subsequently, the structures were subjected to energy minimization and geometry optimization using the Universal Force Field (UFF) to achieve the most stable conformation. Finally, the optimized ligands were converted to PDBQT format using AutoDock Tools v1.5.7, enabling their use in docking simulations. This pre-processing ensured accurate prediction of ligand protein binding interactions and binding affinities during docking studies.

Docking interactions and binding affinity

The docking interaction analysis revealed distinct binding affinities of neem phytochemicals with each cytokine

target (Fig. 4). For MIP-1 α , azadirachtin exhibited a binding energy of -6.8 kcal/mol, nimbolide showed a stronger interaction at -7.6 kcal/mol, while nimbin bound with -6.5 kcal/mol, indicating nimbolide as the most favorable binder to this chemokine. In the case of MIP-1 β , the binding affinities were comparatively lower, with azadirachtin at -6.0 kcal/mol, nimbolide at -6.4 kcal/mol, and nimbin at -5.7 kcal/mol, suggesting moderate but weaker interactions compared to other cytokines. For IL-1 β , azadirachtin bound with -6.5 kcal/mol, nimbolide displayed a high affinity of -7.5 kcal/mol, and nimbin showed -6.8 kcal/mol, again highlighting nimbolide as the strongest candidate. When docked with IL-6R, azadirachtin had a binding energy of -6.6 kcal/mol, nimbin bound at -6.8 kcal/mol, whereas nimbolide exhibited the most favorable binding at -7.8 kcal/mol, making it the

top performer against this receptor. Finally, with TNF- α , azadirachtin showed a relatively high binding energy of -7.1 kcal/mol, nimbolide matched with a strong value of -7.5 kcal/mol, and nimbin bound with -6.6 kcal/mol. Overall, these individual results consistently identified nimbolide as the most potent binder across all five cytokines, followed by azadirachtin with selective strong affinities (notably for TNF- α), and nimbin as a moderate but broad-spectrum interactor (Fig. 4; Table 2).

LigPlot⁺ interaction analysis

LigPlot⁺ analysis was carried out to visualize the molecular interactions and binding modes of neem phytochemicals with pro-inflammatory cytokines and chemokines (Fig. 5). The 2D interaction diagrams highlighted both

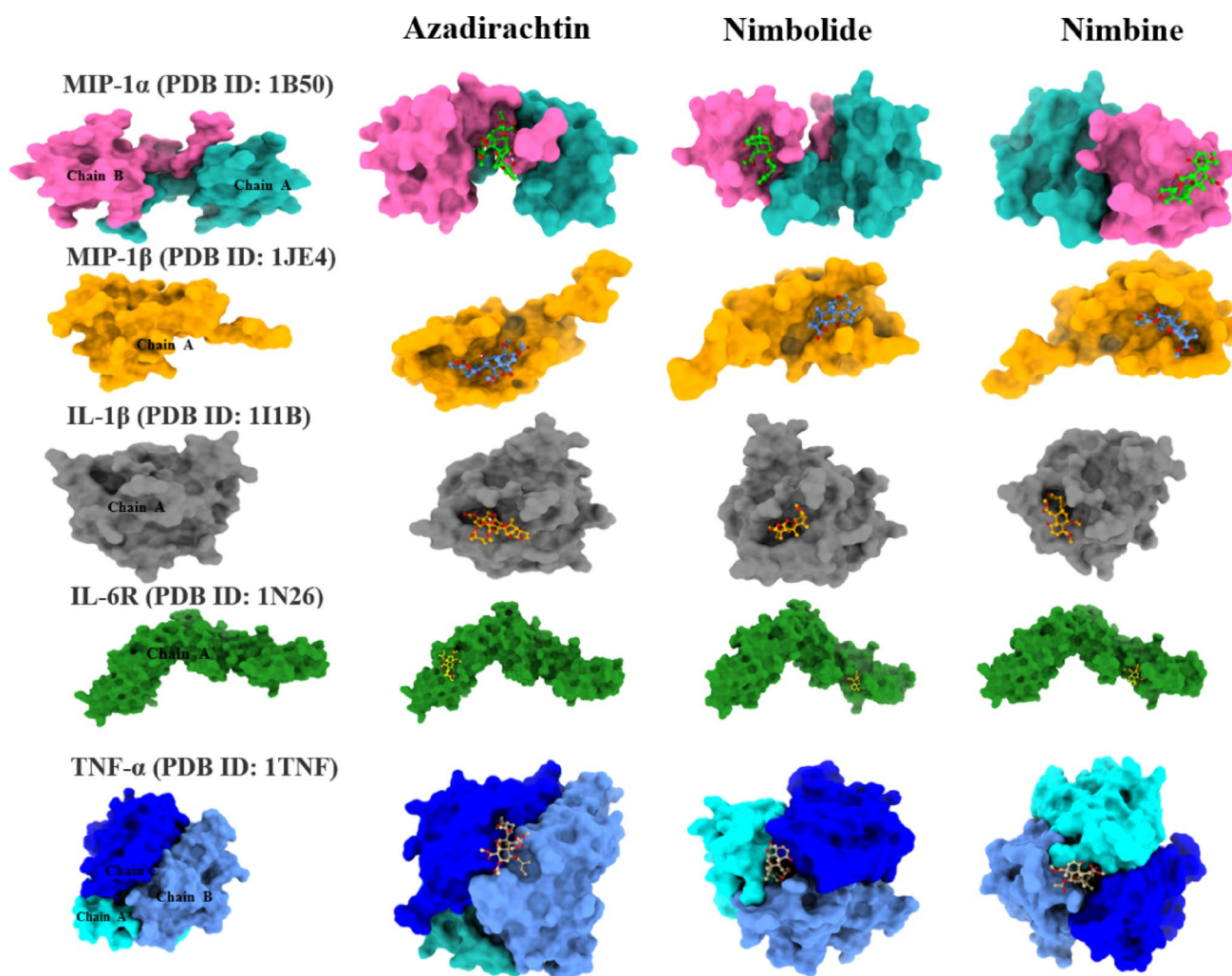


Fig. 4 Molecular docking analysis of three phytochemicals Azadirachtin, Nimbolide, and Nimbine against key inflammatory cytokines and receptor proteins: MIP-1 α (PDB ID: 1B50), MIP-1 β (PDB ID: 1JE4), IL-1 β (PDB ID: 1I1B), IL-6R (PDB ID: 1N26), and TNF- α (PDB ID: 1TNF). Each protein is visualized in surface representation

with distinct color-coded chains, and the respective ligand is shown in stick representation within the binding pocket. From left to right, the columns represent ligand binding for Azadirachtin, Nimbolide, and Nimbine across all target proteins

Table 2 Comparative molecular docking results of azadirachtin, nimbolide, and nimbin against selected pro-inflammatory cytokines and chemokines, showing binding energies (kcal·mol⁻¹), key interacting residues, and interaction types from molecular docking and LigPlot+ analysis

Phytocompound	Target protein	Key amino acid interactions	Interaction types	Binding energy (kcal/mol)
Azadirachtin	MIP-1 α	Asp6(B), Thr8(B), Ser32(B), Ala37(A), Glu38(A)	Hydrogen bonding, hydrophobic interactions	-6.8
	MIP-1 β	Arg14(A), Tyr15(A), Thr16(A), Cys12(A), Ser14(A)	H-bonding, electrostatic, van der Waals	-6.0
	IL-1 β	Arg4(A), Ser8(A), Tyr9(A), Asp6(A)	H-bonding, polar contacts	-6.5
	IL-6R	Thr6(A), Trp7(A), His8(A), Arg21(A), Leu64(A)	H-bonding, hydrophobic	-6.6
	TNF- α	Tyr59(B), Arg106(B), Gln102(A), Glu23(B)	H-bonding, electrostatic	-7.1
Nimbolide	MIP-1 α	Arg47(B), Ile19(B), Ala36(A), Thr43(B), Phe23(B)	Hydrophobic, van der Waals	-7.6
	MIP-1 β	Leu20(A), Thr16(A), Tyr15(A), Cys12(A), Ser14(A)	H-bonding, hydrophobic	-6.4
	IL-1 β	Ser51(A), Ser8(A), Tyr9(A), Asp6(A)	Polar contacts, H-bonding	-7.5
	IL-6R	Leu123(A), Phe64(A), Ser124(A)	H-bonding, van der Waals	-7.8
	TNF- α	Arg106(B), Glu104(A), Thr105(C)	H-bonding, electrostatic	-7.5
Nimbin	MIP-1 α	Trp57(B), Lys68(B), Tyr61(B), Glu18(B), Arg42(A)	H-bonding, hydrophobic	-6.5
	MIP-1 β	Tyr68(A), Pro87(A), Ser72(A), Glu64(A), His70(A)	Polar, H-bonding	-5.7
	IL-1 β	Tyr68(A), Glu64(A), Ser72(A), Leu65(A)	H-bonding, van der Waals	-6.8
	IL-6R	Thr124(A), Ser123(A), Glu122(A), Leu65(A)	Hydrophobic, H-bonding	-6.8
	TNF- α	Arg106(B), Gln102(A), Thr105(C), Gly108(B)	H-bonding, electrostatic	-6.6

Binding energies reflect ligand protein affinity, with more negative values indicating stronger interactions. Residue-level details and interaction types are derived from docking interaction diagrams (LigPlot+), confirming stability of the docked complexes

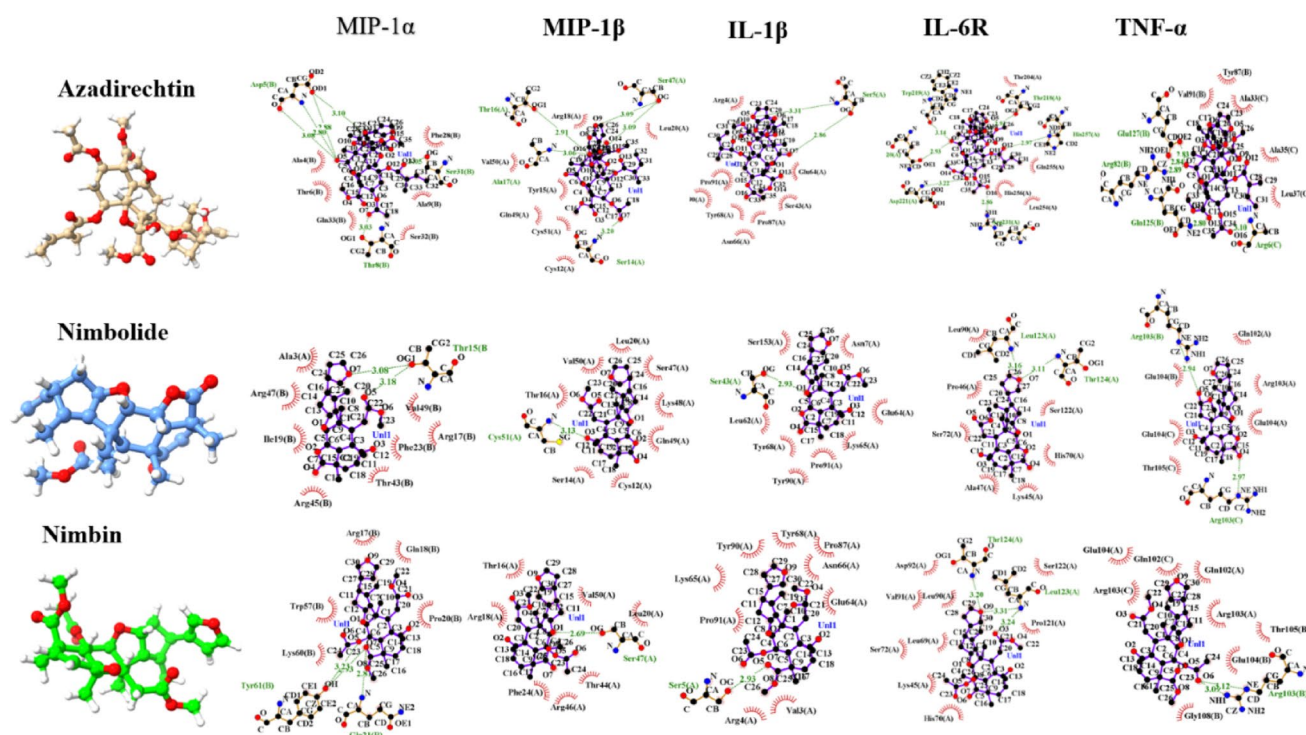


Fig. 5 Molecular docking interactions of neem-derived phytochemicals (Azadirachtin, Nimbolide, and Nimbin) with pro-inflammatory cytokines and receptors (MIP-1 α , MIP-1 β , IL-1 β , IL-6R, and TNF- α). The left panel represents the 3D structures of the ligands, while

the right panels illustrate 2D ligand–protein interaction maps (LigPlot+ interaction analysis) highlighting hydrogen bonds (green dashed lines), hydrophobic interactions (red arcs), and interacting amino acid residues

hydrogen bonds and hydrophobic contacts, providing deeper insights into ligand-protein stability. For Azadirachtin, binding to TNF- α was stabilized by multiple hydrogen bonds with residues Arg106, Gln102, and Tyr59, along with hydrophobic contacts involving Leu57 and Gly108. In IL-6R, hydrogen bonding with Thr6 and Arg21 complemented hydrophobic interactions with Trp7 and Leu64, while its complex with MIP-1 α engaged residues Asp6, Ser32, and Glu38 through hydrogen bonds, indicating strong specificity. Nimbolide displayed a distinct interaction profile characterized by fewer but stronger hydrogen bonds, supplemented by extensive hydrophobic contacts. In IL-1 β , nimbolide formed hydrogen bonds with Ser8, Tyr9, and Asp6, stabilized by hydrophobic residues Val41 and Leu43. With IL-6R, it engaged Leu123 and Ser124 via hydrogen bonding, supported by van der Waals contacts with Phe64. In TNF- α , nimbolide established hydrogen bonds with Arg106 and Glu104, in addition to hydrophobic interactions with Thr105 and Gly108, producing a highly stable docked complex. For Nimbin, LigPlot⁺ diagrams showed consistent but moderate interactions across all targets. In TNF- α , hydrogen bonds were observed with Arg106 and Gln102, accompanied by hydrophobic contacts with Leu57 and Tyr59. Its binding with IL-6R involved Ser123 and Glu122 through polar interactions, while hydrophobic stacking was seen with Leu65. Against MIP-1 β , nimbin interacted via hydrogen bonds with Tyr68 and Ser72, supported by hydrophobic contacts with Pro87 and His70, suggesting balanced stabilization despite lower binding energies. Overall, LigPlot⁺ analysis confirmed that nimbolide formed the most extensive and stable interaction networks, particularly with IL-6R and TNF- α , while azadirachtin demonstrated strong multi-residue hydrogen bonding, and nimbin maintained a broad but weaker interaction spectrum. These findings align with the binding energy values, reinforcing nimbolide as the most promising lead compound for attenuating pro-inflammatory signalling in LF.

Discussion

Comparative analysis of binding affinities among neem compounds

The molecular docking analysis consistently identified nimbolide as the most favorable binder across the five inflammatory targets examined (MIP-1 α , MIP-1 β , IL-1 β , IL-6R, and TNF- α), with the strongest binding affinity observed for IL-6R ($-7.8 \text{ kcal mol}^{-1}$), followed by IL-1 β ($-7.5 \text{ kcal mol}^{-1}$) and TNF- α ($-7.5 \text{ kcal mol}^{-1}$). Azadirachtin displayed

selective high affinity for TNF- α ($-7.1 \text{ kcal mol}^{-1}$) and intermediate interactions with other cytokines, while nimbin produced moderate but broadly distributed affinities (-5.7 to $-6.8 \text{ kcal mol}^{-1}$). These patterns were supported by Lig-Plot⁺ interaction maps: nimbolide engaged targets through strong hydrogen bonds and extensive hydrophobic contacts, azadirachtin demonstrated multi-residue hydrogen bonding, and nimbin formed stable but fewer polar interactions. This hierarchy highlights nimbolide as a lead immunomodulatory candidate, azadirachtin as a selective modulator, and nimbin as a moderate, broad-spectrum interactor.

Potential mechanisms of cytokine modulation in LF pathology

Neem phytochemicals may influence LF pathology by modulating pro-inflammatory cytokines and chemokines at several levels. Direct binding to cytokines (TNF- α , IL-1 β) or receptors (IL-6R) could sterically block ligand–receptor interactions or stabilize inactive conformations, thereby preventing downstream activation of NF- κ B, MAPK, and JAK/STAT3 pathways (Babu and Nutman 2014; Chakraborty et al. 2013). For trimeric TNF- α and inflammasome-activated IL-1 β , ligand binding may disrupt oligomerization or receptor clustering required for high-avidity signaling. Similarly, interactions with MIP-1 α and MIP-1 β could attenuate CCR-mediated leukocyte recruitment, limiting chronic immune infiltration. These extracellular effects may act synergistically with the reported intracellular actions of neem compounds, such as suppression of NF- κ B and MAPK signaling (Kaur et al. 2004; Sultana et al. 2009). Collectively, such modulation could reduce endothelial activation, VEGF-C-driven lymphangiogenesis, fibrosis, and tissue remodeling central pathological processes in chronic LF.

Relevance to host-directed therapy and adjunct treatment strategies

Host-directed therapeutic potential

Host-directed therapies (HDTs) aim to mitigate disease morbidity by modulating host immune responses rather than directly targeting the parasite. The docking results indicate that neem phytochemicals, particularly nimbolide and azadirachtin, possess the capacity to attenuate key inflammatory mediators implicated in lymphatic filariasis pathology (Rajendran et al. 2024). However, despite its promising binding affinity, azadirachtin exhibits poor drug-likeness and low predicted oral bioavailability, which may limit its translational potential unless supported by alternative delivery strategies or formulation approaches. In addition, Lig-Plot interaction analysis suggests that nimbin forms stable

hydrogen bonding and hydrophobic contacts with multiple cytokine targets, indicating its potential role as a moderate but broad-spectrum immunomodulatory compound. By dampening cytokine-driven inflammatory cascades, these phytochemicals may contribute to reducing chronic lymphatic inflammation, fibrosis, and pathological lymphangiogenesis, thereby complementing conventional antifilarial treatment strategies (Bonnah et al. 2023).

Adjunct role with mass drug administration (MDA)

Mass drug administration remains the cornerstone of LF elimination but primarily reduces parasite transmission and microfilaremia, with limited impact on established morbidity (WHO 2023). Neem-derived phytochemicals may be administered through multiple routes depending on their pharmacokinetic properties and therapeutic objectives. Oral administration represents the most feasible approach for systemic immunomodulatory effects, as several neem constituents have previously demonstrated acceptable bioavailability and safety profiles in preclinical studies. However, due to solubility and stability limitations of certain limonoids, advanced delivery strategies such as nanoemulsions, liposomal encapsulation, or polymer-based nanoparticles have been explored to enhance bioavailability and therapeutic efficacy (Rinaldi et al. 2017; Patra et al. 2019). In the context of lymphatic filariasis, neem-derived compounds could therefore be considered as adjunct agents alongside mass drug administration (MDA), with dosing strategies requiring careful optimization through future pharmacokinetic and toxicological investigations.

Safety considerations and immunological balance

While neem-derived compounds such as nimbolide, azadirachtin, and nimbin show promising immunomodulatory potential, their clinical translation requires careful consideration of safety and immunological homeostasis. Excessive inhibition of pro-inflammatory cytokines may reduce the host's ability to control secondary infections or latent pathogens, potentially compromising overall immune competence (Babu and Nutman 2014). Conversely, sub-therapeutic modulation may be insufficient to alleviate tissue inflammation or lymphatic remodeling in chronic LF. Toxicological studies indicate that neem compounds generally exhibit low systemic toxicity at moderate doses; however, high doses of nimbolide and azadirachtin have been associated with hepatotoxicity, gastrointestinal irritation, and reproductive effects in animal models (Subapriya and Nagini 2005). Importantly, computational ADMET predictions suggest favourable oral bioavailability and limited CNS penetration, indicating reduced risk of neurotoxicity,

but these predictions must be corroborated by in vivo pharmacokinetic studies (Daina and Zoete 2016).

Immunological balance is a particular concern in host-directed therapy. Cytokines such as TNF- α , IL-1 β , and IL-6 play dual roles in pathogen clearance and tissue inflammation; thus, selective modulation rather than complete blockade is critical. Strategies such as controlled dosing, temporal targeting during peak inflammatory responses, or nano-formulation-based delivery may allow precise regulation of cytokine activity, minimizing unintended immunosuppression (Fordjour et al. 2025). Additionally, potential drug–herb interactions with standard antifilarial regimens (e.g., diethylcarbamazine, ivermectin, albendazole) must be evaluated, as neem compounds could alter drug metabolism through CYP450 enzyme modulation, affecting efficacy or safety (Gougis et al. 2021). Overall, the therapeutic window for neem phytochemicals requires rigorous preclinical and clinical assessment, ensuring that anti-inflammatory benefits do not compromise host defense mechanisms or long-term health (Ghosh et al. 2026).

Path toward translational validation

To translate these computational findings into therapeutic applications, systematic validation is essential. Previous studies have utilized lymphatic endothelial models and experimental filarial infection systems to investigate inflammatory signalling, lymphangiogenesis, and host–parasite interactions in lymphatic filariasis (Chakraborty et al. 2013; Babu and Nutman 2014; Bennuru et al. 2018). Pharmacokinetic, ADMET, and safety evaluations, coupled with advanced formulation strategies such as nano-encapsulation, will be critical to overcome solubility and delivery barriers common to phytochemicals (Fordjour et al. 2025). If validated, nimbolide and azadirachtin could emerge as affordable, plant-based adjunct therapies for morbidity management in LF-endemic region.

Future perspectives

The present study identifies neem-derived compounds, particularly nimbolide and azadirachtin, as promising lead molecules for modulating pro-inflammatory mediators implicated in LF pathology. In addition, nimbin demonstrated moderate but consistent interaction profiles across multiple cytokine targets, suggesting complementary immunomodulatory potential. Future investigations should aim to validate these in silico predictions through in vitro studies, including cytokine neutralization assays, receptor–ligand competition analyses, and signalling pathway evaluations such as NF- κ B and JAK/STAT inhibition (Islas et al. 2020; Sarkar et al. 2021). Ex

vivo lymphatic endothelial models and in vivo filarial infection systems will be essential to confirm their role in reducing inflammation, lymphangiogenesis, and fibrosis without impairing parasite clearance. Importantly, evaluating the synergistic potential of neem compounds with standard antifilarial drugs may help establish adjunct therapeutic strategies that address both infection control and morbidity management (Hoerauf et al. 2011). Equally critical are pharmacokinetic, bioavailability, and safety studies, including advanced formulation approaches such as nano-encapsulation, to overcome solubility and delivery challenges common to phytochemicals (Patra et al. 2019; Rinaldi et al. 2017; Bag et al. 2026a, b). In the long term, neem phytochemicals could contribute to the development of affordable, host-directed therapies that complement MDA programs, thereby enhancing morbidity control and offering sustainable solutions for LF in resource-limited settings (WHO 2020).

Conclusion

The present study highlights neem-derived phytochemicals, particularly nimbolide and azadirachtin, as promising modulators of pro-inflammatory cytokines and chemokines central to lymphatic filariasis (LF) pathology. In silico docking consistently identified nimbolide as the strongest binder across IL-6R, IL-1 β , and TNF- α , while azadirachtin demonstrated selective but significant affinity for TNF- α , and nimbin showed moderate, broad-spectrum interactions. These findings suggest that neem compounds could mitigate cytokine-driven inflammation, lymphatic dysfunction, and fibrosis, supporting their potential as host-directed adjuncts to complement mass drug administration. However, these findings should be interpreted with caution, as they are based solely on computational predictions and require validation through in vitro and in vivo studies before any therapeutic or clinical applications can be considered. Although computational in nature, the results establish a rational basis for experimental validation through in vitro, ex vivo, and in vivo models. Although the results remain preliminary, they provide a rational basis for further experimental validation through in vitro, ex vivo, and in vivo studies, alongside pharmacokinetic and safety assessments. Ultimately, neem phytochemicals represent affordable, plant-based candidates for integrated LF management, with the promise of contributing to sustainable therapeutic strategies in endemic regions.

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the work, Provided conceptual guidance, and critical revision of the manuscript. Shubhajit Saha assisted in study data interpretation, and critically reviewed the manuscript.

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