Zanthoxylum acanthopodium DC (Andaliman): From Traditional Medicine to Modern Phytotherapy: A Review of Phytochemistry, Bioactivities, and Pharmaceutical Development

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Abstract
Zanthoxylum acanthopodium DC (Andaliman), a spice-bearing shrub native to North Sumatra, Indonesia, possesses a long history of traditional culinary and medicinal use. Its diverse phytochemical profile, including terpenoids, alkaloids, flavonoids, glycosides, tannins, and saponins, forms the basis of its therapeutic potential. This review systematically compiles and analyzes in vitro and in vivo evidence for its broad-spectrum pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, hepatoprotective, nephroprotective, and wound-healing effects. The review emphasizes the correlation between solvent choice and bioactivity, the functions of key active compounds (e.g., limonene, quercetin, and fargesin), and elucidated therapeutic mechanisms. This work identifies critical research gaps in pharmacokinetics, toxicity, and formulation, proposing a strategic roadmap for translational research. This review provides a consolidated scientific foundation to guide the future development of *Andaliman* as a modern therapeutic agent and functional food ingredient.

Keywords: Zanthoxylum acanthopodium; Ethnopharmacology; phytochemistry; pharmacokinetics.

1. Introduction

Southeast Asia, particularly Indonesia, is recognized as a global hotspot of medicinal plant biodiversity, with thousands of species documented for therapeutic applications. The region's deep-rooted tradition of herbal medicine is vital in primary healthcare, yet despite this rich ethnobotanical heritage, the pharmacological efficacy and mechanisms of action remain underexplored (Elfahmi et al. ; Lubis et al. 2022; De Padua et al. 1999; Sangat et al. 2000; RAHMAWATY et al. 2019; Rapoliene et al. 2023). Among these promising species is Zanthoxylum acanthopodium DC, or Andaliman, a spice-bearing shrub of the Rutaceae family found in the highland regions of North Sumatra, Indonesia. Renowned for its distinctive citrus-pepper aroma, Andaliman is a culinary staple (DM R et al. 2021) and is prominent in traditional Indonesian and Indian medicinal systems (Begum et al. 2018). Various plant parts, including the bark, roots, and seeds, have been historically employed to treat ailments such as cholera, digestive disorders, skin infections, and fever (Panjaitan et al. 2021; Bhattacharya et al. 2017; Devi et al. 2015; Sonangda et al. 2019; Syari et al. 2019). Phytochemical analyses have confirmed that *Z. acanthopodium* is rich in diverse secondary metabolites, including alkaloids, terpenoids, flavonoids, glycosides, tannins, and essential oils (Xuliang et al. 2022; SARAGIH et al. 2019). Notably, compounds such as citronellal and limonene are associated with immunomodulatory and antimicrobial properties. Pharmacological studies have validated its antioxidant, anti-inflammatory, antibacterial, antifungal, anticancer, and cardioprotective effects (Gea et al. 2022; Amelia et al. 2020; Ompusunggu et al. 2021).

Despite its rich ethnobotanical history and pharmacological profile, the translational development of *Zanthoxylum acanthopodium* remains constrained. While other species within the *Zanthoxylum* genus have been extensively reviewed, *Zanthoxylum acanthopodium* is underrepresented and critically lacks a synthesis that bridges its documented bioactivities with the significant hurdles to clinical application (Wijaya et al. 2019; Syahputra et al. 2023; Hutapea et al. 2024). Therefore, the primary objective of this review is twofold: first, to systematically consolidate and critically evaluate current knowledge on the plant's ethnobotany, phytochemistry, and diverse pharmacological activities, and second, to provide the first in-depth analysis of the significant transitional gaps, namely, the lack of pharmacokinetic (ADME) and comprehensive toxicological data. By identifying these crucial research gaps, this review proposes a strategic, multidisciplinary research road map to serve as a definitive foundation to guide the development of *Z. acanthopodium* as a standardized, evidence-based phytopharmaceutical and functional food ingredient.

2. Literature search strategy

A systematic literature search was conducted across multiple electronic databases (ScienceDirect, PubMed, Web of Science, Google Scholar, and Baidu Scholar) for publications from January 2000 to December 2024. The search

utilized the keywords: "*Zanthoxylum acanthopodium*," "Andaliman," "phytochemistry," "traditional use," "bioactivity," and "pharmacology." The primary search was supplemented by screening institutional repositories, relevant M.Sc. and Ph.D. dissertations, and reference lists of key articles. Inclusion was limited to peer-reviewed research articles and conference proceedings that reported traditional uses, chemical profiling, or experimental evidence (in vitro/in vivo) of pharmacological activity. Duplicate entries and non-English publications were excluded.

3. Botanical and ethnomedicinal overview

Zanthoxylum acanthopodium DC is a deciduous shrub or small tree from the Rutaceae family, typically reaching 2-3 meters in height.(Sonangda et al. 2019) Its key features include compound pinnate leaves with 5-7 pairs of ovate-lanceolate leaflets, sharp spines on its branches, and small greenish-yellow flowers arranged in panicles (Fig. 1) (RAHMAWATY et al. 2019; Sonangda et al. 2019). The spherical fruits (4-5 mm) transition from reddish-brown to black upon ripening and contain essential oils responsible for the plant's characteristic citrus-like aroma (B Siregar. 2003). Native to the tropical and subtropical highlands of North Sumatra, *Z. acanthopodium* thrives in well-drained, moist soils and demonstrates considerable ecological resilience, making it suitable for wild harvesting and cultivation (Siahaan et al. 2019). The plant holds a significant place in traditional Indonesian and Ayurvedic medicine. The roots are employed to treat gastrointestinal disorders and inflammation; the bark and seeds are used as tonics for fever, cholera, and dyspepsia; and crushed fruits are topically applied for skin ailments. Its essential oils are used as insect repellents and culinary condiments. This extensive ethnomedicinal history suggests that the fruit, bark, and root are rich reservoirs of bioactive compounds, warranting the detailed pharmacological validation explored in this review.

Zanthoxylum acanthopodium has a long and varied history of ethnomedicinal use across Southeast Asia, particularly in North Sumatra, where it serves both a culinary and therapeutic role. Various plant parts, including the roots, bark, seeds, and fruits, are traditionally used to treat numerous conditions. Table 1 comprehensively summarizes these traditional applications, the plant parts used, preparation methods, and the associated health benefits spanning gastrointestinal, inflammatory, antimicrobial, and dermatological domains (Begum et al. 2018; Amelia et al. 2020; Suryanto et al. 2004; Farida et al. 2021; Susanti et al. 2020; Anggraeni. 2020; Majumder et al. 2014; Datta et al. 2013). Beyond its specific therapeutic application, the plant's role in food is notable. In North Sumatran cuisine, the fruits and seeds are a key spice, imparting a pungent, tingling sensation to traditional condiments and meat dishes. This culinary use also extends to food preservation, a practice supported by the known antimicrobial action of essential oils (Frederick et al. 2021). These diverse applications underscore the dual cultural and therapeutic significance of *Z. acanthopodium* and provide a strong rationale for its pharmacological investigation and potential development as a modern functional food and phytomedicine.

Table 1. Traditional uses of *Zanthoxylum acanthopodium*

Traditional application	**Plant part used**	**Use/ application**	**Health or cultural benefit**	**Ref**
Gastrointestinal health	Roots, Bark	Decoctions or toni	Indigestion, diarrhea, crampin stomach discomfort	Farida et al., 2021
Oral care	Bark	Chewing bark	Toothache, antibacterial den hygiene	Susanti et al.,
Culinary use	Fruits, Seeds	Spice, condiment	Pungent taste; used in food preservation	Anggraeni et al., 2020
Respiratory relief	Essential oil, Bark	Inhalation, tonic	Cough, colds, bronchial irritation	Majumder et al., 2014
Antimicrobial/ Antifungal	Essential oil, Bark, Fruits	Topical or oral application	Skin infections, wound abscesses	Amelia et al., Majumder et al., 2014
Inflammatory conditions	Roots, Bark	Decoctions	Inflammation, pain	Datta et al., 2013
Anti-parasitic	Fruits, Seeds	Ingestion	Roundworms, intestinal parasites	Shylla et al., 2022
Insect repellency	Essential oil	Topical, fumigatio	Mosquito and insect repellent	He et al., 2018
Dermatological use	Bark, Essential oil	Topical applicatio	Skin diseases, leprosy, abscesses	Begum et al., 2018
Anticancer	Fruits, Bark	Empirical use	Cancer remedy (modern in vitro eviden supports activity)	Bhattacharya et al., 2017

Fig. 1. Key botanical features of *Zanthoxylum acanthopodium* DC. The figure displays a composite photograph of the plant alongside a schematic summary of its primary morphological characteristics.

4. Phytochemical profile and analysis

Zanthoxylum acanthopodium possesses various secondary metabolites that contribute to its pharmacological activities. Major classes identified in the plant include alkaloids, flavonoids, phenolics, terpenoids, saponins, tannins, coumarins, steroids, and glycosides.(Megawati et al. 2023) The efficiency of extracting these compounds is highly dependent on solvent polarity, a critical factor for isolating bioactive fractions. As the preliminary phytochemical screening of fruit extracts demonstrates (Fig. 2), polar solvents like methanol effectively extract a broad spectrum of compounds (Muzafri et al. 2018). In contact, non-polar solvents such as hexane are more selective for compounds like steroids/triterpenoids, while failing to extract key classes like alkaloids and anthraquinone glycosides. This solvent-dependent profile is fundamental for designing extraction protocols tailored to specific pharmacological investigations (Muzafri et al. 2018).

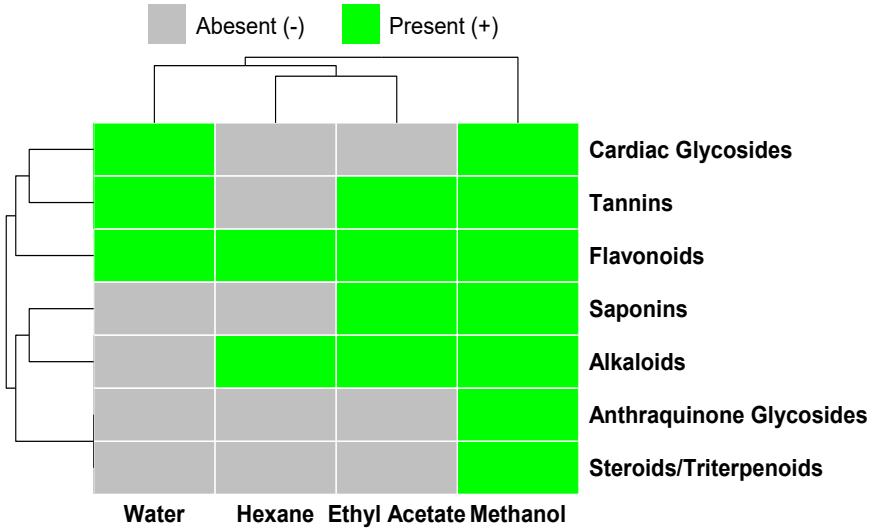

Fig. 2. Heat map of the phytochemical profile of *Zanthoxylum acanthopodium* fruit extracts. Major phytochemical classes' presence (green) and absence (grey) were assessed across four extraction solvents. The diagram on the y-axis indicates hierarchical clustering of phytochemical diversity based on the solvent extraction pattern.

Characterization of these phytochemicals is typically achieved through a combination of extraction and advanced analytical techniques. Steam distillation followed by Gas Chromatography-Mass Spectrometry (GC-MS) is standard for volatile components, particularly essential oils. This approach has been crucial for identifying bioactive monoterpenes such as citral and limonene, which are responsible for their antibacterial properties (Panjaitan et al. 2021). For non-volatile constituents (alkaloids and flavonoids), Soxhlet extraction using polar and semi-polar solvents (e.g., methanol, ethanol, ethyl acetate) is commonly paired with Liquid Chromatography-Mass Spectrometry (LC-MS) (Pradeep et al. 2014). The high resolution of LC-MS enables detailed profiling even at low concentrations (Sibero et al. 2020). The complementary use of GC-MS and LC-MS enables comprehensive chemical characterization, facilitating the correlation of phytochemical profiles with observed pharmacological effects.

6. Pharmacological properties

Zanthoxylum acanthopodium exhibits a broad spectrum of pharmacological effects that have garnered growing scientific attention (Wen et al. 2024). Bioactivity studies confirm its potential in modulating oxidative stress, inflammation, microbial infections, cancer progression, and cardiovascular dysfunction. These therapeutic effects are primarily attributed to its diverse secondary metabolites, including flavonoids, terpenoids, alkaloids, and

essential oils. The following subsections summarize key pharmacological activities, supported by *in vitro* and *in vivo* studies, highlighting bioactive constituents, experimental models, assay outcomes, and mechanisms of action.

6.1 Antioxidant activity

The antioxidant potential of *Z. acanthopodium* has been extensively validated through multiple chemical assays. For example, methanol extracts of the fruit, rich in flavonoids and phenolics such as quercetin and neohesperidin, exhibited notable free radical scavenging activity in the CUPRAC assay (IC_{50} = 86.58 µg/mL). In contrast, the plant's essential oil, containing high levels of D-limonene and geranyl acetate, displayed more potent activity in the DPPH assay (IC_{50} = 28.37 µg/mL). Such variations are expected, as different antioxidant assays (CUPRAC, DPPH, FRAP, and ABTS) rely on distinct redox mechanisms and are sensitive to differences in radical species, solvent polarity, and incubation periods (Rahmi et al. 2023; Assyfa et al. 2024). Despite these assay-sensitive differences, the collective evidence suggests that *Z. acanthopodium* is a potent source of natural antioxidants. This capacity is fundamental to many other therapeutic effects and supports its potential applications in preventing and managing oxidative stress-related disorders.

6.2 Anti-inflammatory activity

The anti-inflammatory potential of *Z. acanthopodium* has been validated through nitric oxide (NO) inhibition assays in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. Bark extracts obtained using petroleum ether and ethyl acetate strongly suppressed NO production (by 70% at 40 µg/mL), significantly outperformed n-butanol extracts. Bioassay-guided fractionation of the petroleum ether extract via high-performance counter-current chromatography (HPCCC) isolated the active lignans, fargesin and epieudesmin. Mechanistically, these compounds significantly downregulated the expression of pro-inflammatory cytokines TNF-α and IL-1β, indicating the potent immunomodulatory potential of the extracts.

The plant's essential oils also exhibited significant anti-inflammatory properties, though activity varies with geographical origin. Oils from fruits collected in China (EOZC) showed superior efficacy (IC_{50} = 16 µg/mL), comparable to the control L-NMMA (IC_{50} = 12.2 µg/mL). In contrast, oil from Myanmar (EOZM) showed moderate activity (IC_{50} = 37 µg/mL). This variation is likely attributed to differences in their phytochemical profiles, particularly in the relative abundance of key monoterpenes and sesquiterpenes (limonene, β-myrcene, and terpinen-4-ol) (Yang et al. 2022; Fan et al. 2023). These findings underscore *Z. acanthopodium* as a promising source of natural anti-inflammatory agents, with bioactivity contribution from its non-volatile lignans and essential oil components.

6.3 Antimicrobial activity

Z. acanthopodium demonstrates substantial antimicrobial activity, with compounds derived from the plant's extracts, essential oils, and even its resident microbiome capable of combating various bacterial and fungal pathogens (Julistiono et al. 2018). The plant's activity is frequently selective, with multiple preparations demonstrating potency against distinct classes of microbes. The following subsections provide a more detailed account of these discoveries.

6.3.1. Antifungal activity

The antifungal potential of *Z. acanthopodium* has been demonstrated against various fungi and dermatophytes. Among solvent-based preparations, the petroleum ether (PE) extract exhibits notable efficacy against pathogens like *C. albicans* and *C. krusei*, while other extracts showed more moderate activity (Devi et al. 2015). The plant essential oils, however, display particularly potent and geographically variable activity (Fig. 3). Essential oil sourced from China (EOZC) is highly effective against a broad spectrum of dermatophytes, with the most vigorous activity observed against *E. floccosum* (MIC_{90} = 26.3 µg/mL). In contrast, oil from Myanmar (EOZM) is consistently less potent across the same fungal strains. The difference in potency is linked to their distinct chemotypes; superior activity of EOZC is attributed to higher levels of limonene and β-myrcene, which disrupt fungal membranes and inhibit fungal spore germination. Conversely, the more moderate activity of EOZMs is likely due to dominant compounds, terpinen-4-ol and γ-terpinene, which interfere with fungal membrane permeability and enzymatic processes.(Fan et al. 2023)

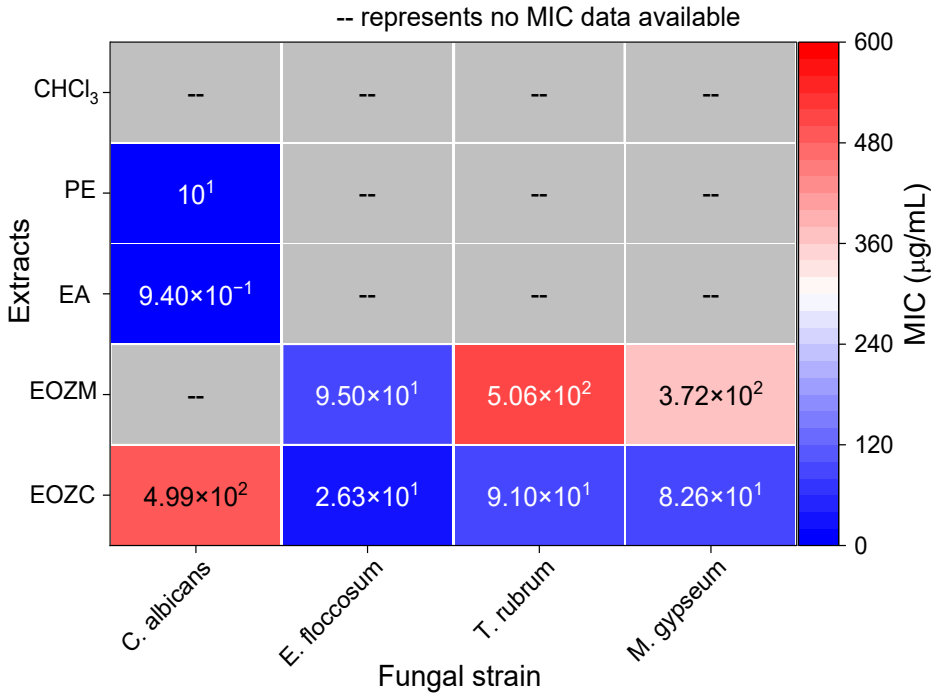

Fig. 3. Minimum Inhibitory Concentration (MIC) values of *Zanthoxylum acanthopodium* extracts against fungal strains. Lower MIC values (in blue) indicate stronger antifungal activity. EOZC (China) exhibits potent efficacy, particularly against *E. floccosum*, compared to EOZM (Myanmar) and solvent extracts. "--" denotes missing or unreported MIC values.

6.3.2. Antibacterial activity

The antibacterial potential of *Z. acanthopodium* has been demonstrated against a range of clinically relevant pathogens, with bioactive compounds originating from both the plant itself and its resident endophytic bacteria (Table 2). Notably, endophytic bacteria isolated from the plant have shown significant promise.(Muzafri et al. 2022) For instance, several root-derived endophytes exhibited vigorous, selective activity against *B. subtilis*, with Minimum Inhibitory Concentration (MIC) values confirming their efficacy.(Rizqoh et al. 2024) Methanolic fruit extract showed limited activity against marine pathogens (e.g., *Tenacibaculum maritimum* and *Vibrio)* but exhibited cytotoxicity toward murine P388 leukemia cells (IC_{50} = 19.14 µg/mL), indicating potential anticancer relevance (Sibero et al. 2020).

Solvent-based extracts of various plant parts also display significant antibacterial efficacy. The extracts obtained with polar solvents (ethanol and ethyl acetate) consistently show the most potent and broad-spectrum activity against both gram-positive (*B. subtilis)* and gram-negative (*S. typhi)*, attributed to a rich profile of alkaloids, steroids, tannins, and saponins (Sitanggang et al. 2019; Sihombing et al. 2019; Ira et al. 2022). Notably, essential oils derived from the stems (ZACS) display high selectivity against gram-negative bacteria like *Escherichia coli* (MIC = 128 µg/mL), an effect attributed to their high content of monoterpenes and sesquiterpenes, which are known to disrupt bacterial outer membranes more effectively than in Gram-positive bacteria (Diep et al. 2023).

Table 2. Antibacterial activity of *Zanthoxylum acanthopodium* extracts against selected bacterial strains using various solvents and bioassays.

Plant Part	Extract Source	Target Bacteria	Methods	Ref
Root	Methanolic	*Bacillus subtilis*	Kirby-Bauer disc diffusion, MIC	Rizqoh et al., 2024
Root	Ethyl acetate	*Bacillus subtilis*	Antagonist test, disc diffusion	
Stem	Ethyl acetate	*Bacillus subtilis*	Antagonist test, MIC	
Fruit	Methanolic	*Tenacibaculum maritimum; Vibrio alginolyticus; V. anguillarum, V. Harveyi; Murine P388* leukemia cells.	Kirby-Bauer disc diffusion, XTT cytotoxicity assay	Sibero et al., 2020
Fruit	Ethyl acetate	*Escherichia coli*	Agar diffusion, MIC	Sitanggang et al., 2019
Fruit	Ethanol	*Bacillus subtilis; Salmonella typhi*	Disc diffusion method	Sihombing et al., 2019
Fruit	Ethanol	*Staphylococcus aureus; Staphylococcus epidermidis*	MIC, Disc diffusion	Ira et al., 2022

Fruit	Various solvents (Ethyl acetate, Methanol, Hexane, Aqueous)	*Escherichia coli*	Disc diffusion	Muzafri et al., 2022

6.3.3. Activity of purified compounds

Beyond crude extracts and oils, bioactivity-guided isolation has identified potent purified compounds. Two novel antimicrobial compounds isolated from the fruit, MKC-1 and MKC-2, exhibited broad-spectrum activity against bacteria and fungi (Table 3). Notably, MKC-2 demonstrated superior potency, with larger inhibition zones and lower MIC values than MKC-1 across multiple strains. The high, broad-spectrum efficacy of MKC-2 establishes it as a promising lead compound for natural antimicrobial drug development (Thu et al.).

The evidence suggests that *Z. acanthopodium* exhibits significant potential as an antimicrobial agent. Its activity is diverse, demonstrating antifungal properties against dermatophytes and antibacterial efficacy against Gram-negative bacteria. The discovery of potent, broad-spectrum purified compounds like MKC-2, alongside the observed activity in its essential oils and even its associated microbiome, further enhances this plant's promise as a source for novel antimicrobial agents to combat drug-resistant bacteria and fungi.

6.4. Antiviral and Larvicidal Activities

Essential oils extracted from *Z. acanthopodium* fruits collected in China (EOZC) and Myanmar (EOZM) have shown promising antiviral properties, particularly against the dengue virus (DENV) and Zika virus (ZIKV). The plant's potential for a dual-pronged approach, targeting both the virus and its mosquito vector, makes it a subject of considerable interest. The essential oil from Myanmar (EOZM) exhibited superior antiviral efficacy compared to the oil from China (EOZC) (Fig. 4). Against DENV, EOZM is highly potent (IC_{50} = 13 µg/mL) and exhibits an affordable safety profile, indicated by a high selectivity Index (SI = 14). This potency surpasses that of the standard antiviral reference compound (NITD008). While also active against ZIKV, its efficacy is more moderate (IC50=94 µg/mL). In contrast, EOZC is significantly less effective, showing only moderate antiviral activity against DENV (IC_{50} = 184.86 µg/mL; SI = 4.35) and no inhibition of ZIKV. This difference in potency is likely attributed to their distinct phytochemical profiles, with the superior activity of EOZM linked to its higher abundance of limonene and β-myrcene, which are known to interfere with viral envelope integrity and host-virus fusion mechanisms (Yang et al. 2022).

Beyond its direct antiviral action, Z. *acanthopodium* essential oils also possess larvicidal properties. Prior studies have reported larvicidal activity of its oils against the larvae of mosquito vectors, further supporting their potential role in dengue vector control programs. This complementary activity, like the oil's rich monoterpene content, supports a potential dual-application strategy, inhibiting viral replication while simultaneously controlling the vector population.

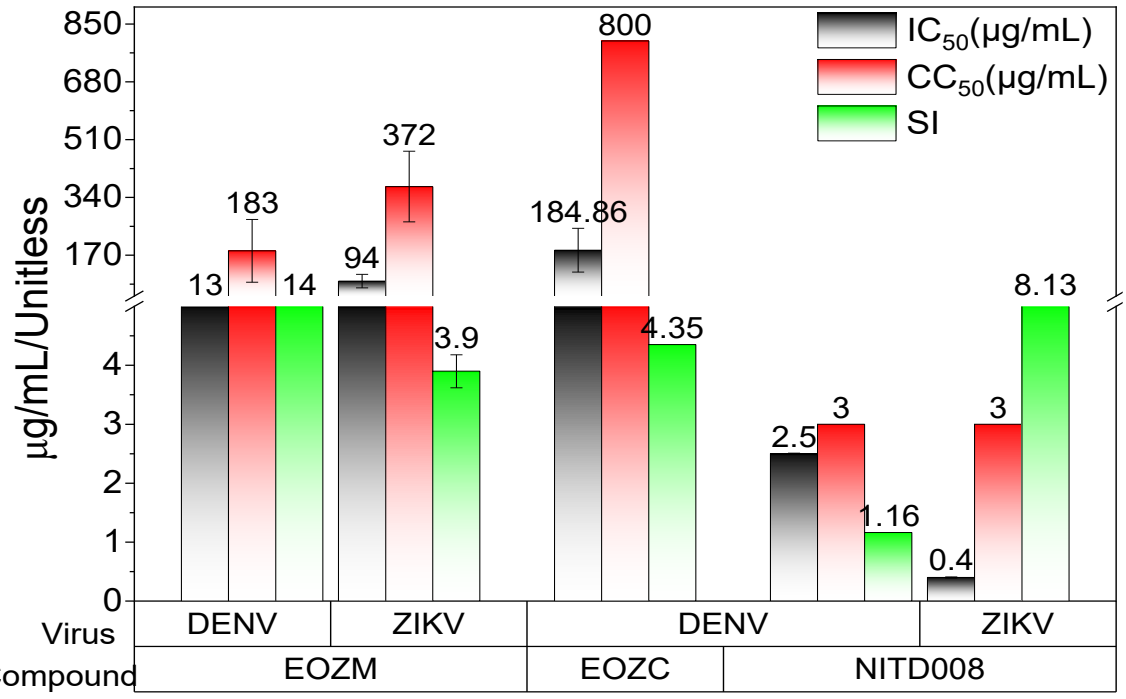

Fig. 4. Comparative IC_{50}, CC_{50}, and SI values of *Zanthoxylum acanthopodium*-derived antiviral agents against DENV and ZIKV. IC_{50} and CC_{50} are expressed in µg/mL, while SI is dimensionless. Lower IC_{50} and higher SI values indicate superior antiviral efficacy.

Further strengthening its role in vector control, the essential oil of *Zanthoxylum acanthopodium* has demonstrated potent larvicidal effects against two key malaria vectors, including *Anopheles anthropophagus* and *Anopheles sinensis*. In WHO-standard bioassays, the oil induced dose-dependent larval mortality, with 24-hour LC_{50} values of 36.00 mg/L and 49.02 mg/L. GC-MS analysis of the oil identified estragole (15.46%) and eucalyptol (10.94%) as primary active

components; both compounds exhibited comparable toxicity against larvae (He et al. 2018). These results establish the essential oil as a sustainable botanical alternative to synthetic pesticides for use in malaria-endemic regions.

Table 3. Comparative IC_{50} and MIC values of Zanthoxylum acanthopodium essential oils and purified compounds against bacterial and fungal strains, with classification of antimicrobial efficacy.

Sample	Microbial Strain	IC50 (µg/mL)	MIC (µg/mL)	Activity classification	Ref
ZACL (Leaves)	*Staphylococcus aureus*	>512	512	*Minimal inhibitory effect*	Diep et al., 202
	Bacillus subtilis	>512	>512	*Ineffective*	
	Lactobacillus fermentum	>512	>512	*Ineffective*	
	Escherichia coli	89.83 ± 1.15	512	*Moderate efficacy*	
	Pseudomonas aeruginosa	320.0 ± 3.56	512	*Low efficacy*	
	Salmonella enterica	>512	>512	*Ineffective*	
	Candida albicans	433.45 ± 4.29	>512	*Minimal antifungal effect*	
ZACS (Stems)	*Staphylococcus aureus*	>512	512	*Minimal inhibitory effect*	
	Bacillus subtilis	490.06 ± 4.82	>512	*Minimal efficacy*	
	Lactobacillus fermentum	>512	>512	*Ineffective*	
	Escherichia coli	83.06 ± 1.08	128	*Moderate to high efficacy*	
	Pseudomonas aeruginosa	291.31 ± 2.63	512	*Low efficacy*	
	Salmonella enterica	>512	>512	*Ineffective*	
	Candida albicans	192.0 ± 2.25	512	*Minimal antifungal effect*	
MKC-1	*Bacillus pumilus*	ND	19.4	*Medium Activity*	Thu et al., 2024
	Bacillus subtilis	ND	16.77	*Medium Activity*	
	Candida albicans	ND	17.5	*Medium Activity*	
	Escherichia coli	ND	18.72	*Medium Activity*	
	Pseudomonas aeruginosa	ND	22.4	*High Activity*	
	Salmonella typhimurium	ND	17.27	*Medium Activity*	
MKC-2	*Bacillus pumilus*	ND	23.2	*High Activity*	
	Bacillus subtilis	ND	22.64	*High Activity*	
	Candida albicans	ND	22.1	*High Activity*	
	Escherichia coli	ND	22.72	*High Activity*	
	Pseudomonas aeruginosa	ND	27.5	*High Activity*	
	Salmonella typhimurium	ND	22.01	*High Activity*	

**ND represents not determined.*

6.5. Anticancer activity

Zanthoxylum acanthopodium extracts have shown broad-spectrum cytotoxicity against various cancer cell lines, attributed to a rich profile of secondary metabolites, including flavonoids, alkaloids, saponins, tannins, and triterpenoids (Harahap et al. 2018). These compounds disrupt cancer signalling pathways by inducing apoptosis, promoting cell cycle arrest, and inhibiting metastasis, with key findings summarized in Table 4. The anticancer effects have been documented across several major cancer types. In the breast cancer model, activity highly depends on the solvent extract. At the same time, crude ethanol extracts show only moderate cytotoxicity against MCF-7 cells (IC_{50} = 221.31 µg/mL) (Arsita et al. 2019). Against T47D cells, fruit's ethyl acetate fraction (EAF) induces G0/G1 cell cycle arrest (IC_{50} = 48.94 µg/mL) via cyclin D1 and p53 upregulation (D Satria et al. 2019). Similarly, the EAF displayed potent cytotoxicity against 4T1 cells (IC_{50} = 54.48 µg/mL), likely due to its high phenolic and flavonoid content.(R Rosidah et al. 2019) Another EAF has been shown to inhibit 4T1 cell migration and induce G2/M phase arrest by suppressing key markers of metastasis like COX-2 and VEGFR-2**.** The ethanol extracts also showed moderate activity against HepG2 liver cancer cells (IC_{50} = 122.65 µg/mL), with apoptosis likely driven by flavonoids and tannins. In colorectal cancer models, ethanol extracts exhibited potent activity against HCT-116 and WiDr cell lines (IC_{50} = 94.64 and 95.61 µg/mL), RT-PCR analysis confirming that activity is driven by apoptosis via

upregulation of the pro-apoptotic Bax/Bcl-2 ratio (Tala et al. 2022; Napitupulu et al. 2022). A consistent trend observed across these studies is that ethyl acetate fractions consistently demonstrate higher cytotoxic potency than crude ethanol extracts, suggesting that the most active compounds have a semi-polar character. The ability of these extracts and their constituents to induce cell cycle arrest, modulate tumour markers, and promote apoptosis highlights *Z. acanthopodium* as a promising source of phytochemicals for anticancer drug development. Future work should focus on compound isolation, structural characterization, and *in vivo* validation to support translational potential.

Table 4. Cytotoxic activity of Zanthoxylum acanthopodium extracts and purified fractions against various cancer cell lines, including associated IC_{50} values, primary and secondary metabolites, and experimental methods employed.

Cell Line	IC_{50} (µg/mL)	Secondary Metabolites	Method	Ref
MCF-7	221.31	Alkaloids, triterpenoids, flavonoids, tannins, phenols, and saponins	MTT Assay	Arsita et al., 2019
T47D	48.94	Alkaloids, tannins, saponins, and flavonoids	MTT Assay, Flow Cytometry, Immunocytochemistry	Satria et al., 2019
4T1	54.48	Tannins, saponins, alkaloids, and flavonoids	MTT Assay	Rosidah et al., 2019
HepG2	122.65	Saponins, alkaloids, flavonoids, and tannins	MTT Assay	Tala et al., 2022
HCT-116	94.64	Alkaloids, Tannins, Saponins, and Flavonoids	MTT Assay, RT-PCR	Napitupulu et al., 2022
WiDr	95.61	Tannins, saponins, alkaloids, and flavonoids	MTT Assay, RT-PCR	
4T1	48.1	Tannins, Triterpenoids, Alkaloids, and Flavonoids	MTT Assay, Flow Cytometry, Wound Healing, qRT-PCR	Harahap et al., 2018

6.6 Cardioprotective activity

Z. acanthopodium exhibits promising cardioprotective effects, particularly in mitigating doxorubicin-induced cardiotoxicity, primarily driven by severe oxidative stress. This activity was validated in a preclinical Wistar rat model where doxorubicin (20 mg/kg, i.p) induced myocardial injury. Subsequent oral administration of hydroalcoholic and ethyl acetate extracts (300 mg/kg for nine days) effectively counteracted the damage. The extracts produced a marked reduction in cardiac injury biomarkers (BNP, CK-MB, cTnT), restoring them to levels comparable to groups treated with standard antioxidants such as rutin and vitamin E. These biochemical findings were corroborated by histopathological examination, which confirmed myocardial preservation via significantly reduced cellular necrosis, myocytolysis, and vascular congestion in the extract-treated groups. This potent action is attributed to the plant's rich content of antioxidant phytochemicals, including flavonoids and alkaloids, which scavenge reactive oxygen species (ROS). By preserving myocardial integrity and reducing oxidative load, *Z. acanthopodium* extracts show promise as a natural therapeutic agent for minimizing or preventing drug-induced cardiotoxicity (Dalimunthe et al. 2024; Sihotang et al. 2016).

6.7. Wound healing activity and tissue regeneration

Z. acanthopodium has emerged as a promising agent for tissue regeneration, particularly when incorporated into advanced wound dressings using modern formulation technologies. For instance, micro-colloidal Andaliman (MZA), rich in flavonoids, terpenoids, and tannins, was incorporated into bacterial cellulose (BC) to create a bioactive scaffold. In *in vivo* rat wound models, these BC-MZA composites significantly accelerated healing. The optimal formulation results in complete wound closure by Day 18, with notable improvement in bacterial clearance, re-epithelialization, and tissue remodelling. These effects are attributed to the anti-inflammatory and antioxidant properties of plants' phytochemicals, which promote wound contraction and reduce infection risk (Pasaribu et al. 2020). The plant's therapeutic potential is further highlighted in diabetic burn injury models using nano-formulated essential oils. Daily topical application of 5% nano-formulation led to significant upregulation of Vascular Endothelial Growth Factor (VEGF), a key mediator of angiogenesis and tissue repair. Macroscopically, this enhanced neovascularization and cellular proliferation translated to ~90% wound closure by Day 14, comparable to standard commercial wound care products (Xuliang et al. 2022; Manurung et al. 2021). These studies underscore the integration of *Z. acanthopodium* into modern nanotechnology platforms, harnessing its phytochemical synergy for wound healing. This approach offers a viable pathway toward developing natural, plant-based alternatives to synthetic wound therapies.

7. Pharmacokinetics and Metabolism

Despite extensive research into its pharmacology, direct pharmacokinetic (PK) and ADME (absorption, distribution, metabolism, excretion) data for *Z. acanthopodium* constituents remain limited, representing a critical knowledge gap (Satria et al. 2023). Insights can, however, be drawn from related species. Major phytoconstituents, including flavonoids and alkaloids, are known to undergo extensive hepatic metabolism via cytochrome P450 (CYP450) enzymes. Specifically, studies on species like *Z. nitidum* show that alkaloids such as magnoflorine and skimmianine exhibit good oral bioavailability and sustained plasma retention in rodent models (Purba et al. 2017). This indicates alkaloid-rich fractions of *Z. acanthopodium* may share these favourable PK traits. Since its extracts are bioactive in vitro at physiologically relevant concentrations, dedicated PK investigations are essential to bridge the gap between in vitro efficacy and potential in vivo application (Panggabean et al. 2020).

A comprehensive pharmacokinetic profiling program is essential to assess its clinical viability. Key research priorities include: (i) quantitative bioavailability studies using LC-MS/MS or UPLC methods; (ii) metabolite identification and metabolic pathway mapping; (iii) pharmacokinetic-pharmacodynamic (PK-PD) modeling to correlate systemic exposure with therapeutic outcomes; and (iv) *in vitro* assays for CYP450 enzyme and drug transporter (e.g., P-glycoprotein) interactions. Elucidating these ADME properties is essential in transitioning *Z. acanthopodium* from a traditional ethnobotanical resource to a clinically validated phytopharmaceutical.

8. Toxicology and Safety Assessment

Toxicological evaluation is a critical prerequisite for the clinical development of Zanthoxylum *acanthopodium* phytotherapeutics. Acute toxicity studies indicate a relatively high safety threshold; methanolic fruit extracts produced no mortality at doses up to 5000 mg/kg, and the nano-formulated version demonstrated a high LD_{50} of 9.807 g/kg in rodent models. However, subacute exposure reveals potential risks that temper this potentially acute profile. Despite high LD_{50}, histopathological examinations have revealed dose-dependent changes in vital organs, including the liver, lungs, heart, and brain. Furthermore, subacute administration (200-1000 mg/kg over 28 days) resulted in physiological and biochemical alterations, including reduced weight gain, hematological disruptions, and clear evidence of hepatic and renal cellular damage (Situmorang. 2020; Shylla et al. 2022).

A particularly significant concern identified in subacute studies is potential reproductive toxicity. At higher doses, extracts were found to decrease sperm count and viability and to induce morphological abnormalities. This suggests that certain phytoconstituents may impair reproductive health, a finding that warrants extensive further investigation. In summary, *Z. acanthopodium* extracts exhibit low acute toxicity; these findings underscore the potential for organ-specific and reproductive risks associated with prolonged or high-dose exposure. Future studies should focus on dose optimization, extract standardization, long-term toxicity studies, and reproductive toxicology profiling to ensure safety for clinical and functional food applications.

9. Conclusion and Future Perspectives

While *Zanthoxylum acanthopodium* possesses a promising pharmacological profile, several critical knowledge gaps hinder its complete translation from ethnobotanical use to evidence-based phytopharmaceutical. Mechanistically, while bioactivity is established, the precise molecular targets and signalling pathways for many of its effects remain uncharacterized. From a translation perspective, a near-complete lack of pharmacokinetic (ADME) data limits any rational dose optimization or safety assessment. Furthermore, significant variability in phytochemical profiles, arising from plant origin, solvent polarity, and extraction techniques, complicates the standardization and reproducibility outcomes. Finally, the safety profile is incomplete, and comprehensive chronic and reproductive toxicity studies are needed before human clinical trials can be considered.

A strategic, multidisciplinary research roadmap is essential to address these limitations and unlock the full potential of Z. acanthopodium. Future work must prioritize elucidating molecular mechanisms employing biology approaches (e.g., transcriptomics, proteomics, metabolomics). This must be paired with comprehensive in vivo ADME studies and physiologically based pharmacokinetic (PBPK) modelling to understand the systemic fate of key constituents. To overcome the issues of variability and bioavailability, research should focus on developing advanced drug delivery systems, such as nanoemulsions and phytosomes, and establishing standardization protocols using defined phytochemical markers (e.g., limonene fragesin). The preclinical safety profile must be completed through long-term toxicology studies before proceeding to carefully designed Phase I clinical trials to assess safety, tolerability, and potential drug or herb interactions.

By systematically addressing these gaps, the scientific community can successfully transition Z. acanthopodium from a plant of rich ethnobotanical tradition into a source of validated next-generation phototherapeutics. Exploring its potential in novel applications, including antimicrobial wound care dressings, botanical insecticides, and synergistic dung combinations, will further solidify its place in modern medicine and environmental health.

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