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PHYTOCHEMICAL PROFILING, ANTIOXIDANT AND ANTIMICROBIAL EVALUATION OF LEAF EXTRACTS OF *ZIZIPHUS NUMMULARIA* (BURM.F.) WIGHT & ARN.: PHYTOCONSTITUENTS, PHARMACOLOGICAL EVIDENCE AND FUTURE PERSPECTIVES

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ABSTRACT

Ziziphus nummularia (Burm.f.) Wight & Arn. (family Rhamnaceae) is a medicinal shrub widely spread in dry and semi dry regions of south Asia and used for different pharmacological action such as gastrointestinal disorders, fever, pain, inflammation, skin disorder and infections. This species of the plant has significant phytochemical importance because of its characterstic cyclopeptide alkaloids together with different metaboloites such as flavanoids, phenolic compounds, tannins, saponins, glycosides, triterpenoids and other secondry metabolites. Pharmacological activity confirmed different action such as antioxidants, antimicrobial, anti-inflammatory, analgesic, antidiabetic and anticancer activities, although there magnitude effects varies with plant part, geographical origin, extraction solvent, fractionation procedure and experimental model. Leaf extract are contain diverse phenolic and flavonoid constituents and cyclopeptide alkaloids have demonstrated antioxidant and pharmacological activities. Recent HPLC-PDA-MS/MS-based an ethanolic leaf extract showed phytochemical variety and identified fractions with antioxidant and antiproliferative activity against triple-negative breast cancer cells. More recent studies also reported anti-inflammatory effects of leaf extracts through modulation of COX-2, iNOS, nitric oxide, ROS, TNF-α, IL-6 and NF-κB/MAPK-related pathways. However, antimicrobial confirmation remains moderately highlighting the need of standardization methods using minimum inhibitory concentration (MIC), minimum bactericidal concentration/minimum fungicidal concentration (MBC/MFC), appropriate controls and well prepared extracts. This review summarizes the botanical, ethnomedicinal, phytochemical and pharmacological evidence for *Z. nummularia*, with particular emphasis on leaves.

KEYWORDS: *Ziziphus nummularia*, Rhamnaceae, cyclopeptide alkaloids, flavonoids, phenolics, antioxidant, antimicrobial, phytochemical profiling

INTRODUCTION

Medicinal plants remain important source of diverse secondary metabolites and contribute to discovery of pharmacologically active compounds. Medicinal shrub of this plant adapted to dry environment, Ziziphus nummularia have extensive traditional use and chemically diverse metabolite profile. Ziziphus nummularia belongs to the family Rhamnaceae and is associated with dry and semi dry regions of the Indian subcontinent area. Pharmacological applications include treatment of fever, gastrointestinal disorders, pain, inflammation, skin disorder and infections. Phytochemical confirmation have identified cyclopeptide alkaloids as one of the characteristics chemical group of the species, accompanied by flavonoids, phenolic compounds, tannins, saponins, glycosides and triterpenoid constituents [1-3]. A comprehensive 2022 review concluded that Z. nummularia have a broad pharmacological profile such as antioxidant, antimicrobial, anti-inflammatory, analgesic, antidiabetic and anticancer activities [1]. The pharmacological importance of the species is associated with chemical diversity. However, different results reported in different studies are not always directly compare because different parts of plant, extraction with different solvents, concentrations, geographical region and biological model have been used. Therefore an activity reported for root bark or fruit should not automatically be recognized to the leaves.

This distinction is particularly important for research focused on leaf extracts. Recent work using ethanolic *Z. nummularia* leaves combined chromatographic fractionation with HPLC-PDA-MS/MS analysis and demonstrated both chemical diversity and biological activity, providing stronger evidence for the potential of leaves as a source of bioactive metabolites [4]. The objective of this review is therefore to critically summarize the phytochemical and pharmacological evidence for *Z. nummularia*, emphasizing leaf-derived evidence and identifying opportunities for standardized antioxidant and antimicrobial evaluation.

Botanical Description and Distribution

Ziziphus nummularia (Burm.f.) Wight & Arn. is a small, thorny, highly branched shrub belonging to the family Rhamnaceae. It is adapted to hot, dry and semi-arid environments and is frequently encountered in grazing lands, scrublands and arid landscapes. The plant generally develops into a bushy shrub with numerous branches and characteristic spines. Leaves are simple, alternate to subopposite, relatively small and rounded to broadly ovate, with a characteristic venation pattern. Flowers are small and inconspicuous, while the fruits are drupaceous and become yellowish to brownish on maturation. The species is distributed predominantly in arid and semi-arid regions of India and neighbouring parts of South Asia and the Middle East. Its ability to tolerate water stress and high temperatures contributes to its ecological importance in dryland environments [1,5]. The taxonomic identity of plant material is important in phytochemical research because differences in species identification, geographical origin and environmental conditions may contribute to variation in metabolite profiles and biological activity.

Ethnomedicinal Importance

Traditional use of *Z. nummularia* involves several plant parts, including leaves, roots, bark, fruits and seeds. Traditional applications have included gastrointestinal disorders, diarrhoea, dysentery, fever, cough, inflammatory conditions, pain and skin disorders. Leaf preparations have been traditionally used for cough and cold, fever-related conditions and external treatment of cuts, boils and other skin problems. Leaf preparations have also been associated with treatment of inflammatory and painful conditions [6]. Root and bark preparations have been traditionally used for gastrointestinal and inflammatory disorders, whereas fruits have been used as food and in several traditional preparations. These uses provide an ethnopharmacological rationale for investigating the plant; however, traditional use should be regarded as a basis for scientific investigation rather than proof of clinical efficacy. Importantly, pharmacological findings from one plant part cannot automatically be generalized to another. For example, anticancer and anti-inflammatory investigations involving root bark should be interpreted separately from recent leaf studies.

Phytochemical Composition

Phytochemical investigations indicate that *Z. nummularia* contains several major classes of secondary metabolites, including:

- cyclopeptide alkaloids
- flavonoids
- phenolic compounds
- tannins
- saponins
- glycosides
- triterpenoids
- sterols
- other minor specialized metabolites.

Cyclopeptide alkaloids represent one of the most characteristic chemical groups of *Z. nummularia*. The species has also yielded flavonoid and phenolic constituents that may contribute to antioxidant and other pharmacological properties [1,2]. Modern analytical approaches have expanded the known chemical diversity. LC-ESI-MS/MS has been used to investigate metabolite distribution in *Z. nummularia*, while HPLC-PDA-MS/MS analysis of leaf extracts has demonstrated multiple metabolites in crude extracts and chromatographic fractions [4,7].

Table 1. Major phytochemical classes reported in *Ziziphus nummularia*

S. No.	Phytochemical class	Representative examples	Reported plant parts	Possible biological relevance
1	Cyclopeptide alkaloids	Nummularine and related cyclopeptide alkaloids	Leaves, stem bark	Analgesic, anti-inflammatory and other pharmacological effects
2	Flavonoids	Flavonoid glycosides, including luteolin derivatives	Leaves, fruits and other parts	Antioxidant, anti-inflammatory and anticancer potential
3	Phenolics	Phenolic acids and related compounds	Leaves, fruits, bark	Radical scavenging and reducing activity
4	Tannins	Hydrolysable/condensed phenolic constituents	Leaves, bark, fruits	Antioxidant and antimicrobial potential

5	Saponins	Triterpenoid/steroidal saponin-type constituents	Leaves and other parts	Membrane-associated and pharmacological effects
6	Glycosides	Diverse glycosidic metabolites	Leaves, fruits and other parts	Variable biological activity
7	Triterpenoids	Pentacyclic triterpenoid derivatives	Roots, bark, leaves	Anti-inflammatory and cytotoxic potential
8	Sterols	Plant sterol constituents	Leaves and other parts	Possible membrane and metabolic effects
9	Other metabolites	Amino acids, organic acids and specialized metabolites	Various parts	Species- and tissue-dependent effects

Cyclopeptide Alkaloids

Cyclopeptide alkaloids are among the most characteristic constituents of the genus *Ziziphus*. In *Z. nummularia*, several nummularine-type compounds have been reported. Tuenter et al. used advanced chromatographic and spectroscopic techniques to isolate seven cyclopeptide alkaloids from *Z. nummularia* and *Z. spina-christi*. The identified compounds included nummularine-U, spinanine-B, spinanine-C, mauritine-F, nummularine-D, nummularine-E and amphibine-D. Three compounds were reported as previously undescribed [2]. Earlier pharmacological work specifically investigated a cyclopeptide alkaloid fraction isolated from *Z. nummularia* leaves. The fraction demonstrated anti-inflammatory effects in experimental models and significant antinociceptive effects in acetic-acid-induced writhing, tail-flick and hot-plate assays [6]. These findings support the importance of cyclopeptide alkaloids as chemical markers of the species. Nevertheless, assigning a particular pharmacological effect exclusively to a single alkaloid requires isolated-compound studies, appropriate controls and mechanistic confirmation.

Flavonoids, Phenolics, Tannins, Triterpenoids and Other Constituents

In addition to cyclopeptide alkaloids, *Z. nummularia* contains several classes of polyphenolic and terpenoid compounds. Flavonoids and phenolics are particularly relevant to antioxidant investigations because their hydroxyl groups can participate in electron- and hydrogen-transfer reactions. Recent leaf investigations have used total phenolic content (TPC), total flavonoid content (TFC), HPLC-PDA-MS/MS and chromatographic fractionation to characterize the chemical composition of leaf extracts [4]. The 2024 leaf study reported substantial TPC/TFC and identified numerous metabolites in crude extract and fractionated material. Triterpenoids and related constituents are also important because several *Ziziphus* species contain structurally diverse triterpenes with anti-inflammatory and cytotoxic properties. However, evidence obtained from other *Ziziphus* species or from non-leaf parts of *Z. nummularia* should not be directly presented as proof of activity in *Z. nummularia* leaves.

Antioxidant Activity

Oxidative stress is associated with excessive production of reactive oxygen and nitrogen species and insufficient endogenous antioxidant defenses. Plant phenolics and flavonoids may contribute to chemical antioxidant activity through radical scavenging and reducing mechanisms. Earlier investigations reported antioxidant activity for methanolic and acetone extracts of *Z. nummularia* leaves, including DPPH and superoxide radical-scavenging activity and reducing power [1]. More recent work has strengthened this evidence. Bhardwaj et al. reported antioxidant activity of *Z. nummularia* using multiple chemical assays, including DPPH, reducing power, hydrogen peroxide scavenging, phosphomolybdate and hydroxyl-radical assays [8]. The 2024 leaf-fractionation study further demonstrated DPPH antioxidant activity in the ethanolic crude leaf extract and its active fractions [4]. More recently, fractions from a methanolic leaf extract were evaluated in the context of oxidative-stress reduction and anti-inflammatory activity, with the chloroform fraction demonstrating notable DPPH activity [9].

Table 2. Summary of antioxidant evidence for *Ziziphus nummularia*

S. No.	Plant material/extract	Assay/model	Major observation	Interpretation
1	Leaves, methanolic extract	DPPH, superoxide, reducing power	Significant radical-scavenging/reducing activity reported	Supports leaf antioxidant potential
2	Leaves, acetone extract	Radical-scavenging assays	Significant antioxidant activity	Solvent-dependent activity
3	Leaves, ethanolic extract	DPPH	Strong antioxidant activity reported	Consistent with polyphenol/flavonoid contribution

4	Leaf chromatographic fractions	DPPH	Selected fractions showed substantial activity	Fractionation may enrich active constituents
5	Methanolic leaf fractions	DPPH	Chloroform fraction showed notable activity	Supports fraction-dependent antioxidant effects
6	Fruit extracts	DPPH and other assays	Antioxidant activity reported	Useful species-level evidence but not leaf-specific
7	Root/bark extracts	Various chemical assays	Antioxidant effects reported	Evidence should not be generalized directly to leaves

Antimicrobial Activity

Antimicrobial activity has been reported for several extracts and fractions of *Z. nummularia*. Activity has been observed against both Gram-positive and Gram-negative bacteria in different studies, although results vary according to extraction solvent, plant part, microbial strain and assay methodology [1,10–13]. Leaf extracts may contain phenolics, flavonoids, tannins, saponins and alkaloids capable of interacting with microbial membranes, enzymes or intracellular targets. However, the available evidence is less standardized than the antioxidant literature. A particularly relevant study evaluated a methanolic *Z. nummularia* preparation against vancomycin-resistant *Staphylococcus aureus* isolates and reported MIC values in the sub-mg/mL range depending on the isolate [12]. The study also used TLC and GC-MS to investigate phytochemical constituents.

Table 3. Representative antimicrobial evidence for *Ziziphus nummularia*

S. No.	Plant material	Extract/fraction	Test organism(s)	Main finding	Evidence level
1	Leaves	Methanolic/organic extracts	Various bacterial strains	Antibacterial activity reported	In vitro
2	Leaves/plant extracts	Different solvent extracts	Gram-positive and Gram-negative bacteria	Activity varied with solvent and organism	In vitro
3	Methanolic plant extract	Methanol	VRSA isolates	MIC values reported from 0.39–0.781 mg/mL for selected isolates	In vitro
4	Roots	Extracts	*Mycobacterium tuberculosis* H37Rv	Antibacterial activity investigated	In vitro
5	Various plant parts	Organic/aqueous extracts	Bacteria and fungi	Variable inhibition reported	In vitro
6	Leaf-derived Ag nanoparticles	*Z. nummularia* leaf extract-mediated AgNPs	Bacterial/fungal organisms	Enhanced antimicrobial activity reported	Nanomaterial-assisted in vitro evidence

Because zone-of-inhibition values are strongly influenced by diffusion characteristics, future leaf studies should prioritize broth microdilution-based MIC determination and, where appropriate, MBC/MFC determination [14,15].

Proposed Mechanisms of Antimicrobial Activity

The antimicrobial activity of *Z. nummularia* is likely to involve multiple mechanisms rather than a single molecular target. Phenolic compounds and flavonoids may interact with microbial membranes, alter membrane permeability and interfere with essential enzymes. Tannins can interact with proteins and may contribute to inhibition of microbial enzymes and cell-surface functions. Saponins may affect membrane integrity because of their amphiphilic nature. Alkaloids may interact with nucleic acids, enzymes or membrane-associated processes.

Anti-inflammatory and Analgesic Activity

Anti-inflammatory and analgesic effects represent some of the better documented pharmacological properties of *Z. nummularia*. Goyal et al. investigated the cyclopeptide alkaloid fraction isolated from leaves and reported dose-dependent inhibition of experimental paw oedema as well as significant antinociceptive effects. The fraction showed activity in peripheral and central analgesic models [6]. Recent research has provided more mechanistic evidence. Abdallah et al. reported that an ethanolic leaf extract reduced COX-2 and iNOS expression and decreased NO, ROS, TNF-α and IL-6 production in LPS-stimulated RAW 264.7 macrophages. The study also indicated modulation of NF-κB, STAT3 and MAPK-related pathways [16]. Kaundal et al. further evaluated methanolic leaf fractions using in vitro assays and a complete Freund's adjuvant-induced arthritis model, providing additional evidence for antioxidant and anti-inflammatory activity of leaf-derived fractions

[9]. Together, these studies suggest that leaf constituents may influence inflammatory mediator production and oxidative-stress pathways. Nevertheless, clinical efficacy and safety remain to be established.

Antidiabetic and Metabolic Potential

Antidiabetic activity has been reported for *Z. nummularia* in experimental investigations. Proposed mechanisms include antioxidant activity, modulation of carbohydrate-metabolizing enzymes and improvement of glucose-related metabolic parameters. A 2025 study by Bhardwaj et al. investigated phytochemical composition, antioxidant properties and antidiabetic potential of *Z. nummularia*. Flavonoids, alkaloids, tannins, saponins and phenolic compounds were detected, and multiple antioxidant assays supported the biological potential of the extracts [8]. However, the antidiabetic evidence should be interpreted cautiously. Chemical enzyme-inhibition assays and animal studies do not establish efficacy in human diabetes. Future work should combine enzyme assays with cellular glucose-utilization models, appropriate animal models, pharmacokinetic assessment and toxicity studies.

Anticancer Potential

Interest in the anticancer potential of *Z. nummularia* has increased in recent years. Earlier studies involving root bark extracts reported cytotoxic and anticancer effects in experimental cancer models [17,18]. These findings demonstrate species-level anticancer potential but should not be directly attributed to leaves. Importantly, recent research has generated direct leaf evidence. Abdallah et al. investigated an 80% ethanolic leaf extract and chromatographically separated fractions. The crude extract and particularly Fraction 6 reduced viability of MDA-MB-231 triple-negative breast cancer cells. The study reported effects on cell-cycle progression, apoptosis, autophagy, migration, invasion and adhesion [4]. A separate 2024 study investigated extracts of *Z. nummularia* in several cancer cell models. The ethanolic extract demonstrated notable activity against KAIMRC2 cells, and experimental observations indicated disruption of the microtubular network. Luteolin-7-O-glucoside was identified as an important candidate metabolite in computational analyses, although these findings require further experimental validation [19]. Thus, the anticancer evidence is promising but remains predominantly preclinical.

Phytochemical–Pharmacological Relationship

The pharmacological profile of *Z. nummularia* is probably the result of interactions among multiple chemical classes rather than a single constituent. Phenolic compounds and flavonoids are strongly associated with chemical antioxidant capacity. Cyclopeptide alkaloids have been associated with analgesic and anti-inflammatory effects. Triterpenoids and flavonoids may contribute to anti-inflammatory and cytotoxic effects, while tannins, saponins, alkaloids and phenolics may contribute to antimicrobial activity.

Table 4. Qualitative phytochemical–pharmacological relationship

S. No.	Phytochemical group	Antioxidant relevance	Antimicrobial relevance	Anti-inflammatory/analgesic relevance	Anticancer relevance
1	Cyclopeptide alkaloids	Possible indirect contribution	Possible	*Strongly investigated*	Preliminary/compound-dependent
2	Flavonoids	*Strong*	Moderate	*Strong*	*Potentially important*
3	Phenolics	*Strong*	Moderate–strong	Moderate–strong	Potential
4	Tannins	Strong	*Moderate–strong*	Potential	Potential
5	Saponins	Moderate	Moderate	Potential	Potential
6	Triterpenoids	Moderate	Potential	*Strong potential*	Potential–strong for selected compounds
7	Sterols	Limited direct evidence	Limited	Potential	Potential
8	Glycosides	Compound-dependent	Compound-dependent	Compound-dependent	Compound-dependent

Recent Research Progress (2022–2025)

Research from **2022–2025** has progressed from preliminary phytochemical screening toward advanced chromatographic profiling, metabolomics, cellular models, and mechanism-based pharmacological evaluation. The 2022 comprehensive review summarized the major phytoconstituents and pharmacological activities of *Z. nummularia* [1]. In 2024, leaf-focused studies combined fractionation with HPLC-PDA-MS/MS and demonstrated anticancer activity against triple-negative breast cancer cells [4], while another study identified luteolin-7-O-glucoside as a potential tubulin-binding anticancer candidate [19]. By 2025, research further expanded to antioxidant/antidiabetic effects, macrophage-based anti-inflammatory mechanisms, and experimental arthritis models, strengthening the pharmacological evidence for *Z. nummularia* [8,9,16].

Table 5. Selected research developments in *Ziziphus nummularia*, 2022–2025

S. No.	**Year**	**Study focus**	**Plant material**	**Major contribution**
1	2022	Comprehensive phytochemical/pharmacological review	Multiple plant parts	Consolidated phytochemical and pharmacological evidence
2	2023	Antimicrobial investigation	Plant extract	Additional evidence for antibacterial potential
3	2024	Leaf fractionation and LC-MS/MS	Leaves	Chemical profiling plus antioxidant and anticancer evaluation
4	2024	Anticancer/tubulin investigation	Extracts	Identified luteolin-7-O-glucoside as a candidate anticancer metabolite
5	2025	Antioxidant/antidiabetic investigation	*Z. nummularia* extracts	Multiple antioxidant assays and antidiabetic evaluation
6	2025	Anti-inflammatory macrophage study	Leaves	COX-2/iNOS, NO, ROS, TNF-α, IL-6 and signaling pathways investigated
7	2025	Experimental arthritis study	Methanolic leaf fractions	Antioxidant and anti-inflammatory/anti-arthritic evaluation

Research Gaps and Future Perspectives

Despite increasing evidence, important research gaps remain in *Ziziphus nummularia*. Future studies should emphasize authenticated plant material, standardized extraction procedures, and quantitative phytochemical profiling using TPC/TFC, HPLC, HPTLC or LC-MS/MS. Antioxidant studies should employ multiple complementary assays, while antimicrobial investigations should include MIC, MBC/MFC and appropriate controls. Correlation of phytochemical profiles with biological activity and bioassay-guided fractionation may help identify active constituents. Further mechanistic, toxicity and pharmacokinetic studies are also required to establish the therapeutic potential and safety of *Z. nummularia* leaf extracts.

CONCLUSION

Ziziphus nummularia is a chemically diverse medicinal plant with a long history of ethnomedicinal use and a growing body of experimental evidence supporting antioxidant, antimicrobial, anti-inflammatory, analgesic, antidiabetic and anticancer potential. Cyclopeptide alkaloids represent a characteristic chemical group of the species, whereas flavonoids, phenolics, tannins, saponins and triterpenoids provide additional chemical diversity.

Evidence specifically involving leaves is particularly important. Leaf cyclopeptide alkaloid fractions have demonstrated analgesic and anti-inflammatory effects, while recent ethanolic and methanolic leaf studies have demonstrated antioxidant, anti-inflammatory and anticancer potential. Recent HPLC-PDA-MS/MS-based work has further demonstrated that leaf extracts contain chemically diverse metabolites that may contribute to these activities.

Nevertheless, the current literature remains heterogeneous with respect to extraction procedures, phytochemical standardization, biological models and antimicrobial methodology. Consequently, future research should prioritize authenticated plant material, reproducible extraction, quantitative phytochemical analysis, complementary antioxidant assays, MIC/MBC/MFC determination and chromatographic or mass-spectrometric fingerprinting.

A particularly valuable research direction is the development of a **standardized leaf-extract profile linking phytochemical composition with antioxidant and antimicrobial activity**. Such an approach could provide stronger scientific evidence for the pharmacological potential of *Z. nummularia* and establish a reproducible basis for future isolation, mechanistic and drug-development studies.

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