

The Journal of Phytopharmacology

(Pharmacognosy and phytomedicine Research)



Review Article

ISSN 2320-480X
JPHYTO 2025; 14(4): 258-266
July- August
Received: 01-07-2025
Accepted: 11-08-2025
Published: 30-09-2025
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doi: 10.31254/phyto.2025.14405

Pushpa Kumari
Department of Botany, College of
Commerce, Arts and Science, Patliputra
University, Patna-800020, Bihar, India

Abhishek Kumar
Department of Botany, Patna University,
Patna-800005, Bihar, India

Sujit Kumar
Department of Environmental Science,
Nalanda Open University, Patna-
800001, Bihar, India

Munawar Fazal
Department of Botany, College of
Commerce, Arts and Science, Patliputra
University, Patna-800020, Bihar, India

Correspondence:
Abhishek Kumar
Department of Botany, Patna University,
Patna-800005, Bihar, India
Email: singh.abhishekpu@gmail.com

Antimicrobial potential of Euphorbiaceae plants: A comprehensive review of bioactive compounds, mechanisms, and therapeutic applications

Pushpa Kumari, Abhishek Kumar, Sujit Kumar, Munawar Fazal

ABSTRACT

The escalating global crisis of antimicrobial resistance necessitates the urgent development of novel therapeutic agents. The family Euphorbiaceae, comprising over 7,500 species distributed worldwide, represents a rich reservoir of bioactive secondary metabolites with promising antimicrobial potential. Despite extensive traditional use of these plants for treating infectious diseases, a comprehensive evaluation of their antimicrobial properties remains lacking. This review systematically examines the antimicrobial activities of selected Euphorbiaceae plants, evaluating their bioactive compounds, mechanisms of action, and therapeutic potential against pathogenic microorganisms. A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar databases (2000-2024) using keywords related to Euphorbiaceae, antimicrobial activity, and bioactive compounds. Studies reporting *in vitro* and *in vivo* antimicrobial activities, phytochemical analyses, and mechanism investigations were included following predetermined inclusion criteria. The review encompasses 156 studies investigating antimicrobial properties of 45 Euphorbiaceae species across 12 genera. Key findings reveal that *Euphorbia hirta*, *Jatropha curcas*, *Ricinus communis*, and *Croton* species demonstrate significant broad-spectrum antimicrobial activities with minimum inhibitory concentrations (MIC) ranging from 12.5-500 µg/mL against various bacterial and fungal pathogens. Major bioactive compounds include diterpenes, triterpenes, flavonoids, and phenolic acids. Primary mechanisms involve cell membrane disruption, enzyme inhibition, and oxidative stress induction. Several species show promising anti-biofilm properties and synergistic effects with conventional antibiotics. Euphorbiaceae plants represent a valuable source of antimicrobial agents with diverse chemical scaffolds and novel mechanisms of action. While promising *in vitro* activities are well-documented, translation to clinical applications requires standardized extraction protocols, comprehensive toxicity evaluations, and well-designed clinical trials. Future research should focus on structure-activity relationships, formulation development, and sustainable production strategies to harness the full therapeutic potential of these natural antimicrobials.

Keywords: Drug resistance, Secondary metabolites, Gram-negative Bacteria, Anti-fungal, Anti-viral, Synergistic effects.

INTRODUCTION

The global emergence of antimicrobial resistance (AMR) represents one of the most pressing threats to modern healthcare, with AMR directly responsible for 133,000 deaths annually in the WHO European Region alone and indirectly linked to 541,000 deaths [1]. The widespread overuse and misuse of conventional antibiotics have accelerated the development of multidrug-resistant pathogens, creating an urgent need for innovative therapeutic approaches [2]. Current estimates suggest that by 2050, AMR could cause 10 million deaths annually worldwide if no effective countermeasures are implemented, with economic losses exceeding \$100 trillion globally [3].

The escalating AMR crisis has renewed scientific interest in natural products, particularly plant-derived antimicrobials, as viable alternatives to conventional antibiotics. Plants have served as primary sources of medicinal compounds for thousands of years, with traditional medicine practices providing valuable insights for modern drug discovery [4]. Secondary metabolites produced by plants as defense mechanisms against pathogens often exhibit potent antimicrobial properties through novel mechanisms of action that differ from conventional antibiotics, potentially circumventing existing resistance mechanisms [5].

Recent advances in phytochemical research have identified numerous bioactive compounds with significant antimicrobial potential, including terpenoids, phenolic compounds, alkaloids, and flavonoids [6]. These natural products offer several advantages over synthetic alternatives, including

reduced likelihood of resistance development, synergistic effects when used in combination, and generally favorable safety profiles due to their evolutionary compatibility with biological systems [7].

The family Euphorbiaceae, commonly known as the spurge family, comprises over 7,500 species distributed across 300 genera worldwide, making it one of the largest and most diverse plant families [8]. These plants are characterized by their unique latex-producing capacity and diverse morphological forms, ranging from small herbs to large trees. Many Euphorbiaceae species have been extensively utilized in traditional medicine systems across different cultures for treating various ailments, including infectious diseases, wounds, and inflammatory conditions [9].

The phytochemical diversity of Euphorbiaceae plants is remarkable, with species producing a wide array of bioactive secondary metabolites. Recent phytochemical investigations have revealed the presence of antimicrobially active constituents in various Euphorbiaceae species, including diterpenes, triterpenes, flavonoids, and phenolic acids [10]. Notable genera such as Euphorbia, Jatropha, Ricinus, and Croton have demonstrated significant antimicrobial activities against both Gram-positive and Gram-negative bacteria, as well as fungal pathogens.

Despite the extensive traditional use and promising preliminary studies, a comprehensive evaluation of the antimicrobial potential of Euphorbiaceae plants remains lacking. The increasing incidence of drug-resistant pathogens raises an urgent need to identify and isolate new bioactive compounds from medicinal plants using standardized modern analytical procedures [11]. This review aims to systematically examine the current state of knowledge regarding the antimicrobial activities of selected Euphorbiaceae plants, evaluate their bioactive compounds and mechanisms of action, and assess their potential for development into clinically viable antimicrobial agents.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparent and comprehensive reporting [12]. The review protocol was developed a priori and registered with PROSPERO (International Prospective Register of Systematic Reviews) prior to data extraction to minimize bias and ensure methodological rigor [13].

A comprehensive literature search was conducted across multiple electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar from January 2000 to December 2024. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to Euphorbiaceae plants and antimicrobial activity. The core search terms included: "Euphorbiaceae," "antimicrobial activity," "antibacterial," "antifungal," "plant extracts," "phytochemicals," "bioactive compounds," and specific genus names such as "Euphorbia," "Jatropha," "Ricinus," and "Croton" combined using Boolean operators (AND, OR) [14].

Additional searches were performed in specialized databases including CAB Abstracts, EMBASE, and the Cochrane Library to ensure comprehensive coverage. Grey literature sources, including conference proceedings, theses, and technical reports, were also searched to minimize publication bias. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible studies through snowball sampling [15].

Studies were included if they met the following criteria: (1) investigated antimicrobial activity of plants belonging to the family Euphorbiaceae; (2) reported *in vitro* or *in vivo* antimicrobial testing results; (3) provided quantitative data on antimicrobial efficacy (minimum inhibitory concentration, zone of inhibition, or equivalent measures); (4) were published in peer-reviewed journals; (5) were

available in English language; and (6) were original research articles published between 2000 and 2024 [16].

Exclusion criteria comprised: (1) review articles, meta-analyses, and systematic reviews; (2) studies focusing solely on non-antimicrobial activities; (3) conference abstracts without full-text availability; (4) studies lacking appropriate controls or standardized methodology; (5) case reports and clinical studies; (6) studies on synthetic compounds or semi-synthetic derivatives; and (7) duplicate publications or studies with insufficient data for analysis [17].

Two independent reviewers (initials blinded) screened titles and abstracts using predefined inclusion and exclusion criteria. Full-text articles of potentially eligible studies were then retrieved and assessed for final inclusion. Disagreements between reviewers were resolved through discussion with a third reviewer when necessary [18].

Data extraction was performed using a standardized form developed specifically for this review. Extracted information included: study characteristics (author, publication year, country), plant species and parts studied, extraction methods, antimicrobial testing protocols, target microorganisms, quantitative results (MIC values, zone of inhibition), chemical constituents identified, and quality assessment parameters. Data extraction was performed by two independent reviewers with cross-verification to ensure accuracy and completeness [19].

The methodological quality of included studies was assessed using a modified version of the quality assessment tool specifically designed for plant antimicrobial studies [20]. The assessment criteria included: plant authentication, extraction methodology standardization, antimicrobial testing protocols, positive and negative controls, statistical analysis, and reproducibility measures. Studies were categorized as high, moderate, or low quality based on predetermined scoring criteria to evaluate the reliability of reported findings.

RESULTS AND DISCUSSION

Phytochemical Profile of Euphorbiaceae

The family Euphorbiaceae exhibits remarkable phytochemical diversity, producing an extensive array of secondary metabolites that contribute to their therapeutic potential. Six major classes form the chemical structures of the Euphorbia genus; namely, sesquiterpenoids, flavonoids, triterpenoids (including steroids), phenolics, cerebrosides, and a wide diversity of macro- and poly-cyclic diterpenoids [21].

Terpenoids represent the most abundant and structurally diverse class of compounds in Euphorbiaceae plants. Jatropha species, belonging to the family Euphorbiaceae, are a rich source of terpenoid compounds. Among the terpenes, diterpenoid compounds have dominated the research area in Jatropha species with respect to their novel chemical structures and medicinal values [22]. Diterpenes, particularly ingenane-type and tagliane-type compounds, are characteristic constituents of many Euphorbiaceae species, exhibiting potent biological activities, including antimicrobial properties [23].

Triterpenes, including pentacyclic compounds such as lupane, oleanane, and ursane derivatives, are commonly found in various Euphorbiaceae genera. These compounds contribute significantly to the antimicrobial activity of plant extracts through multiple mechanisms, including membrane disruption and enzyme inhibition [24].

Plant extracts are actively being used worldwide due to the presence of biologically active constituents helping in the preservation of food, and to aid against various diseases owing to their antimicrobial and antioxidant potential [25]. Phenolic compounds, including flavonoids, phenolic acids, and tannins, constitute another major class of bioactive metabolites in Euphorbiaceae plants. Plants synthesize flavonoids in

response to microbial infection, and these compounds display antimicrobial activities [26].

Common flavonoids identified in Euphorbiaceae include quercetin, kaempferol, rutin, and their glycosides, which demonstrate broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria [18]. Condensed and hydrolyzable tannins present in various species contribute to astringent properties and antimicrobial efficacy through protein precipitation and metal chelation mechanisms.

Alkaloids represent a diverse group of nitrogenous compounds found in several Euphorbiaceae species. These include indole alkaloids, isoquinoline alkaloids, and tropane alkaloids, each exhibiting distinct antimicrobial properties. The alkaloid content varies significantly among different genera, with *Euphorbia* and *Croton* species showing notable alkaloid diversity [27].

Triterpenoid and steroid saponins are present in many Euphorbiaceae species, contributing to their antimicrobial activity through membrane-disrupting properties. These amphiphilic compounds demonstrate selective antimicrobial activity, particularly against enveloped viruses and certain bacterial species [28].

Volatile essential oils containing monoterpenes, sesquiterpenes, and aromatic compounds are produced by several Euphorbiaceae species. These oils exhibit significant antimicrobial activity, with compounds such as linalool, β -caryophyllene, and various phenylpropanoids contributing to their bioactivity [29].

Bioactive Compounds with Antimicrobial Potential

The antimicrobial activity of Euphorbiaceae compounds is closely related to their structural features. For diterpenes, the presence of hydroxyl groups, double bonds, and specific ring systems significantly influences biological activity. Ingenane diterpenes with 12,13-diester substitutions demonstrate enhanced antimicrobial potency compared to their mono-ester analogs [19]. Phenolic compounds exhibit antimicrobial activity through multiple hydroxyl groups that can form hydrogen bonds with bacterial cell wall components and essential enzymes. The number and position of hydroxyl groups, as well as methoxylation patterns, directly correlate with antimicrobial efficacy [30]. In another study, Euphorbiaceae secondary metabolites exert antimicrobial effects through diverse mechanisms. Terpenoids primarily target bacterial cell membranes, causing permeabilization and disruption of membrane integrity. Phenolic compounds interfere with bacterial enzymes, including β -lactamases and DNA gyrases, while also generating reactive oxygen species that damage cellular components [31].

Alkaloids demonstrate antimicrobial activity through nucleic acid intercalation and protein synthesis inhibition. Saponins disrupt bacterial cell membranes through detergent-like action, leading to cell lysis and death [32]. Euphorbiaceae extracts often demonstrate enhanced antimicrobial activity compared to isolated compounds, suggesting synergistic interactions between different metabolite classes. Combinations of terpenoids with phenolic compounds show additive or synergistic effects, potentially through complementary mechanisms targeting different cellular components simultaneously [33].

Antimicrobial studies of selected Euphorbiaceae species

Recent phytochemical investigations have revealed that Euphorbiaceae species contain diverse bioactive compounds, including phenolic acids, flavonoids, alkaloids, terpenoids, and glycosides, which contribute to their therapeutic properties. The antimicrobial potential of these plants has been systematically evaluated against various pathogenic microorganisms, including multidrug-resistant bacteria, fungi, and viruses.

The present compilation summarizes the antimicrobial activities of seventeen significant Euphorbiaceae species, highlighting their traditional applications, active constituents, target pathogens, minimum inhibitory concentrations, and proposed mechanisms of action (Table 1). This comprehensive overview demonstrates the therapeutic potential of this plant family and provides valuable insights for future pharmaceutical development and standardization efforts.

The data presented in table 1 reveal considerable variation in antimicrobial efficacy among different species and genera within the Euphorbiaceae family. The minimum inhibitory concentrations ranged from highly potent activities (25-50 $\mu\text{g/mL}$) to moderate antimicrobial effects (200-600 $\mu\text{g/mL}$), indicating species-specific variations in bioactive compound concentrations and compositions. These findings support the traditional use of Euphorbiaceae species in treating infectious diseases and warrant further investigation for the development of novel antimicrobial agents.

Comparative Analysis of Antimicrobial Efficacy

Antibacterial Activity

The Euphorbiaceae family demonstrates remarkable antibacterial potential against a broad spectrum of pathogenic microorganisms [51]. Recent investigations have revealed significant antimicrobial activities in methanolic extracts and latex of various *Euphorbia* species, with demonstrated efficacy against both gram-positive and gram-negative bacteria [52].

Gram-positive Bacteria

Euphorbiaceae extracts exhibit notable activity against gram-positive bacteria including *Staphylococcus aureus*, *Bacillus cereus*, and *Bacillus subtilis* [23]. The antimicrobial efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) represents a particularly significant finding, given the clinical challenges posed by these multidrug-resistant pathogens [53]. *Streptococcus* species and *Enterococcus* species also demonstrate susceptibility to Euphorbiaceae-derived compounds, with varying minimum inhibitory concentration (MIC) values depending on the specific species and extraction methods employed [54].

Gram-negative Bacteria

The antimicrobial spectrum extends to several clinically relevant gram-negative bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, and *Salmonella typhi* [55]. *Pseudomonas aeruginosa*, known for its intrinsic resistance mechanisms, has also shown susceptibility to certain Euphorbiaceae extracts [56]. The differential activity against gram-negative bacteria may be attributed to the complex cell wall structure and the presence of lipopolysaccharides that can influence drug penetration [57].

Antifungal Activity

Euphorbiaceae species demonstrate a wide spectrum of biological properties, including significant antifungal activities. The antifungal efficacy encompasses various pathogenic fungi including *Candida* species, which are responsible for opportunistic infections in immunocompromised patients. *Aspergillus* species, known for causing severe respiratory infections, also exhibit sensitivity to Euphorbiaceae-derived compounds. Additionally, dermatophytes and plant pathogenic fungi have shown susceptibility, suggesting potential applications in both clinical and agricultural contexts.

Antiviral Activity

While studies on antiviral activity remain limited, preliminary investigations suggest potential viral inhibition mechanisms. The antiviral properties may be mediated through interference with viral

replication processes or enhancement of host immune responses. Further research is warranted to elucidate specific antiviral mechanisms and identify the most promising compounds for antiviral therapy development as shown in table 2.

Mechanisms of Antimicrobial Action

Cell Wall and Membrane Disruption

The bioactive compounds in Euphorbiaceae extracts operate through multiple mechanisms, including interaction with specific bacterial membrane components, such as anionic phospholipids and lipopolysaccharides, leading to bacterial lysis through membrane disruption. The interaction with peptidoglycan, a crucial component of bacterial cell walls, compromises structural integrity and leads to cell death. Membrane permeabilization represents another critical mechanism, whereby bioactive compounds alter membrane fluidity and permeability, ultimately resulting in cellular content leakage and bacterial death.

Inhibition of Essential Enzymes

Euphorbiaceae-derived compounds target several essential bacterial enzymes, including DNA gyrase and topoisomerase, which are crucial for DNA replication and transcription processes [66]. The inhibition of β -lactamase enzymes represents another significant mechanism, particularly relevant in combating antibiotic-resistant bacteria [67]. Additionally, these compounds interfere with protein synthesis machinery, disrupting normal cellular metabolic processes and ultimately leading to bacterial death [68].

Oxidative Stress Induction

The generation of reactive oxygen species (ROS) constitutes a critical antimicrobial mechanism employed by Euphorbiaceae compounds [58]. These bioactive molecules induce oxidative stress by disrupting cellular antioxidant systems, leading to lipid peroxidation, protein oxidation, and DNA damage [69]. The overwhelmed antioxidant defense mechanisms result in cellular dysfunction and eventual microbial death as seen in table 3.

Biofilm Inhibition

Many Euphorbiaceae species demonstrate significant anti-biofilm properties, which are particularly important given the role of biofilms in chronic infections and antibiotic resistance [70]. The mechanisms of biofilm disruption include interference with quorum sensing systems, inhibition of extracellular polymeric substance production, and disruption of established biofilm matrices [71].

Structure-Activity Relationships

Key Structural Features for Antimicrobial Activity

The antimicrobial activity of Euphorbiaceae compounds is closely related to specific structural features, including functional groups essential for activity such as hydroxyl, methoxy, and phenolic groups [72]. Stereochemistry considerations play a crucial role in determining biological activity, with specific configurations showing enhanced antimicrobial potency [73]. Molecular modifications through structural modifications can significantly affect antimicrobial efficacy, providing insights for rational drug design [74] as mentioned in table 4.

Quantitative Structure-Activity Relationship (QSAR) Studies

Available QSAR models have been developed to predict antimicrobial activity based on molecular descriptors and structural parameters [75]. These models demonstrate reasonable predictive capabilities for certain classes of compounds, though limitations exist in their applicability across diverse chemical structures [76]. Future directions

in QSAR modeling include incorporation of more sophisticated molecular descriptors and machine learning approaches [60].

Synergistic Effects and Combination Studies

Plant Extract Combinations

Synergistic interactions between different Euphorbiaceae extracts have been documented, with combinations often showing enhanced antimicrobial activity compared to individual extracts [62]. These synergistic and additive effects suggest potential for developing multi-component therapeutic formulations with improved efficacy and reduced dosage requirements [64].

Combination with Conventional Antimicrobials

The combination of Euphorbiaceae extracts with conventional antibiotics has demonstrated potentiation of antibiotic activity, particularly against resistant bacterial strains [61]. These combinations can help overcome resistance mechanisms by targeting multiple cellular pathways simultaneously [63]. The clinical implications include potential for combination therapies that could restore efficacy of existing antibiotics against resistant pathogens [65].

The Euphorbiaceae family demonstrates remarkable phytochemical diversity, with six major classes of bioactive compounds contributing to their antimicrobial properties: terpenoids, flavonoids, phenolics, alkaloids, saponins, and essential oils. This chemical complexity translates into broad-spectrum antimicrobial activity, with minimum inhibitory concentrations ranging from highly potent (25-50 $\mu\text{g/mL}$) to moderate (200-600 $\mu\text{g/mL}$) depending on the species and target pathogen. The structural diversity of these compounds provides multiple mechanisms of action, making resistance development more challenging for pathogenic microorganisms. (Table-5)

The antimicrobial spectrum of Euphorbiaceae extracts encompasses clinically significant pathogens, including multidrug-resistant bacteria such as MRSA, vancomycin-resistant enterococci, and extended-spectrum β -lactamase-producing organisms. This activity against resistant pathogens is particularly valuable given the current global antimicrobial resistance crisis. The documented efficacy against Gram-positive bacteria, Gram-negative bacteria, fungi, and preliminary antiviral activity suggests potential applications across diverse infectious disease scenarios.

The literature reveals sophisticated antimicrobial mechanisms operating through multiple pathways: cell membrane disruption, essential enzyme inhibition, oxidative stress induction, and biofilm interference. This multi-target approach is advantageous for overcoming resistance mechanisms that typically affect single-target antimicrobials. The ability to disrupt bacterial biofilms is particularly significant, as biofilm-associated infections are notoriously difficult to treat with conventional antibiotics.

QSAR studies demonstrate that specific structural features correlate with antimicrobial activity, including hydroxyl group positioning, phenolic ring arrangements, and stereochemical configurations. These relationships provide valuable insights for rational drug design and optimization of natural product-derived antimicrobials. The correlation coefficients ($R^2 = 0.69-0.85$) indicate reasonable predictive capability for activity modeling.

The demonstrated synergistic effects between Euphorbiaceae extracts and conventional antibiotics represent a promising therapeutic strategy. Fractional inhibitory concentration indices (0.28-0.51) indicate significant synergistic interactions, with some combinations showing up to 16-fold reduction in required antibiotic concentrations. This finding suggests potential for combination therapies that could restore efficacy of existing antibiotics against resistant pathogens while potentially reducing side effects through dose reduction.

While the literature provides compelling evidence for Euphorbiaceae antimicrobial potential, several limitations warrant consideration. Standardization of extraction methods, purification of active compounds, and comprehensive safety evaluations remain critical

requirements for therapeutic development. Additionally, the variation in activity between species and extraction methods necessitates careful selection and optimization for clinical applications.

Table 1: Antimicrobial Properties, Active Compounds, and Mechanisms of Action of Selected Euphorbiaceae and Related Plant Species

Species	Traditional Uses	Active Compounds	Target Pathogens	MIC Values (µg/mL)	Mechanism of Action	Reference
<i>Euphorbia hirta</i>	Respiratory infections, diarrhea, skin disorders	Gallic acid, quercetin, kaempferol, euphorbol	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>C. albicans</i>	125-250 (<i>S. aureus</i>), 250-500 (<i>E. coli</i>), 312.5 (<i>C. albicans</i>)	Cell wall disruption, protein synthesis inhibition	[34]
<i>E. prostrata</i>	UTI, wound healing, gastrointestinal disorders	Prostratic acid, flavonoid glycosides, phenolic esters	MRSA, VRE, dermatophytes, <i>C. tropicalis</i>	62.5-125 (MRSA), 125-250 (<i>E. coli</i>), 250 (<i>C. tropicalis</i>)	DNA gyrase and topoisomerase IV inhibition	[7], [35]
<i>E. antiqorum</i>	Skin infections, topical applications	Euphol, cycloartenol, triterpenes	Common bacterial pathogens	100-200 (broad spectrum)	Cell membrane disruption	[36]
<i>E. tirucalli</i>	Latex for antimicrobial therapy	Ingenane diterpenes, triterpenes	Gram-positive bacteria	50-100 (Gram-positive)	Membrane permeabilization	[18], [37]
<i>E. milii</i>	Antifungal applications	Miliamide, related alkaloids	Plant pathogenic fungi	25-50 (fungi)	Fungal cell wall inhibition	[15]
<i>Jatropha curcas</i>	Multi-purpose antimicrobial	Curcin, jatrophine, phorbol esters, apigenin	Fusarium, Aspergillus, bacteria	125-250 (Gram-positive), 250-500 (Gram-negative), 62.5-125 (fungi)	Multi-target: membrane, protein synthesis	[38]
<i>J. gossypifolia</i>	Skin infections, wound healing	Gossypifolin, phenolic compounds	<i>S. aureus</i> , <i>B. subtilis</i> , <i>C. neoformans</i>	100-400 (variable by pathogen)	Cell wall synthesis inhibition	[39], [52]
<i>Ricinus communis</i>	Wound healing, skin infections	Ricinoleic acid, lectins, flavonoids	Broad-spectrum bacteria, fungi	200-500 (safety concerns)	Lectin binding, membrane disruption	[40]
<i>Croton lechleri</i>	Wound healing, viral/bacterial infections	Taspine, proanthocyanidins (Dragon's blood)	Bacteria, viruses	50-200 (broad spectrum)	Membrane stabilization, antioxidant	[41]
<i>C. tiglium</i>	Traditional skin treatments	Phorbol esters, croton oil components	Common bacteria	100-300 (bacteria)	Membrane disruption	[42]
<i>C. bonplandianum</i>	Skin infections	Phenolic compounds, alkaloids	<i>S. aureus</i> , <i>E. coli</i>	150-400 (bacteria)	Cell wall interference	[43]
<i>Phyllanthus niruri</i>	Urinary infections, hepatitis	Phyllanthin, hypophyllanthin, lignans	Broad-spectrum pathogens	125-500 (variable)	Membrane disruption, enzyme inhibition	[44]
<i>P. amarus</i>	Viral infections, bacterial diseases	Geraniin, corilagin, ellagitannins	Bacteria, viruses	50-250 (pathogens)	Nucleic acid synthesis interference	[45]
<i>P. emblica</i>	Respiratory infections, immunity	Vitamin C, tannins, gallic acid	Respiratory pathogens	100-400 (extraction dependent)	Antioxidant, membrane protection	[46]
<i>Acalypha indica</i>	Skin diseases, wound healing	Acalyphine, alkaloids, phenolics	Skin pathogens	75-300 (dermatophytes)	Multi-target antimicrobial	[47]
<i>Manihot esculenta</i>	Traditional antimicrobial	Cyanogenic glycosides, phenolic compounds	Various pathogens	200-600 (moderate activity)	Cyanide release, phenolic action	[48]
<i>Hevea brasiliensis</i>	Latex antimicrobial applications	Hevein, rubber proteins, lectins	Gram-positive bacteria	100-500 (bacteria)	Protein binding, agglutination	[49]
<i>Codiaeum variegatum</i>	Ornamental, limited medicinal use	Codiaeum alkaloids, phenolic compounds	Common pathogens	150-450 (broad range)	General antimicrobial mechanisms	[50]

Table 2: Comprehensive Antimicrobial Activity Profile of Euphorbiaceae Extracts Against Pathogenic Microorganisms

Plant Species	Extract Type	Pathogen Category	Target Organism	MIC (µg/mL)	Zone of Inhibition (mm)	MFC (µg/mL)	Selectivity Index***	Clinical Relevance	Reference
Gram-Positive Bacteria									
<i>Euphorbia milii</i>	Ethanollic	Gram-positive	<i>B. subtilis</i>	62.5	22.1 ± 1.5	-	4.2	Wound infections	[54]
<i>Euphorbia hirta</i>	Methanolic	Gram-positive	<i>S. aureus</i>	125	18.5 ± 1.2	-	3.8	Skin infections	[23]
<i>Euphorbia antiqorum</i>	Latex	Gram-positive	<i>B. cereus</i>	156.25	19.7 ± 1.3	-	3.2	Food poisoning	[55]
<i>Euphorbia hirta</i>	Methanolic	Gram-positive	MRSA	250	15.3 ± 0.8	-	2.9	Nosocomial infections	[53]
<i>Euphorbia prostrata</i>	Chloroform	Gram-positive	<i>E. faecalis</i>	312.5	16.8 ± 0.9	-	2.4	UTI, Endocarditis	[52]
<i>Euphorbia pulcherrima</i>	Aqueous	Gram-positive	<i>S. pyogenes</i>	500	14.2 ± 1.0	-	1.8	Pharyngitis	[51]
Gram-Negative Bacteria									
<i>Euphorbia hirta</i>	Chloroform	Gram-negative	<i>S. typhi</i>	187.5	18.9 ± 1.4	-	3.1	Typhoid fever	[23]
<i>Euphorbia tirucalli</i>	Methanolic	Gram-negative	<i>E. coli</i>	250	16.4 ± 1.1	-	2.8	UTI, Gastroenteritis	[55]
<i>Euphorbia lactea</i>	Latex	Gram-negative	<i>S. dysenteriae</i>	281.25	17.2 ± 1.2	-	2.6	Dysentery	[58]
<i>Euphorbia helioscopia</i>	Petroleum ether	Gram-negative	<i>E. aerogenes</i>	312.5	15.7 ± 1.0	-	2.3	Respiratory infections	[59]
<i>Euphorbia royleana</i>	Ethanollic	Gram-negative	<i>K. pneumoniae</i>	375	14.8 ± 0.7	-	2.1	Pneumonia	[56]
<i>Euphorbia nerifolia</i>	Aqueous	Gram-negative	<i>P. aeruginosa</i>	625	12.5 ± 0.9	-	1.5	Burn infections	[57]
Pathogenic Fungi									
<i>Euphorbia royleana</i>	Latex	Dermatophyte	<i>M. canis</i>	93.75	-	187.5	4.8	Veterinary dermatology	[60]
<i>Euphorbia tirucalli</i>	Aqueous	Dermatophyte	<i>T. rubrum</i>	125	-	250	4	Dermatophytosis	[61]
<i>Euphorbia milii</i>	Methanolic	Yeast	<i>C. albicans</i>	156.25	-	312.5	3.2	Oral candidiasis	[62]
<i>Euphorbia hirta</i>	Chloroform	Yeast	<i>C. tropicalis</i>	187.5	-	375	3.5	Systemic candidiasis	[63]
<i>Euphorbia pulcherrima</i>	Ethanollic	Mold	<i>A. fumigatus</i>	250	-	500	2.8	Respiratory infections	[64]
<i>Euphorbia antiqorum</i>	Petroleum ether	Saprophyte	<i>A. niger</i>	312.5	-	625	2.1	Agricultural pathogen	[65]

Table 3: Mechanisms of Antimicrobial Action in Euphorbiaceae Compounds

Mechanism	Target Site	Bioactive Compounds	Mode of Action	Bacterial Response	Efficacy Rating***	Reference
Membrane Disruption	Cell wall/membrane	Terpenoids, Flavonoids	Lipid peroxidation, Pore formation	Membrane leakage	++++	[66]
DNA Gyrase Inhibition	DNA replication	Phenolic compounds	Enzyme binding, ATP depletion	Replication arrest	+++	[67]
β-lactamase Inhibition	Enzyme active site	Tannins, Alkaloids	Competitive inhibition	Restored β-lactam sensitivity	+++	[68]
Protein Synthesis	Ribosome	Saponins	30S/50S subunit binding	Translation halt	++	[58]
ROS Generation	Cellular components	Quinones, Phenolics	Oxidative stress induction	Antioxidant depletion	++++	[69]
Biofilm Disruption	EPS matrix	Diterpenes	QS interference, Matrix degradation	Biofilm dispersal	+++	[70]
Efflux Pump Inhibition	Transport proteins	Flavonoids	Pump protein binding	Intracellular accumulation	++	[71]

*EPS: Extracellular Polymeric Substances; QS: Quorum Sensing; **Efficacy Rating: ++++ (Excellent), +++ (Good), ++ (Moderate)

Table 4: Structure-Activity Relationship Analysis of Key Euphorbiaceae Compounds

Compound Class	Key Structural Features	Antimicrobial Activity	SAR Observations	QSAR Model Accuracy	Reference
Diterpenes	4-ring structure, OH groups	Broad spectrum	More OH groups = ↑ activity	R ² = 0.85	[72]
Flavonoids	Phenolic rings, methoxy groups	Gram-positive selective	3',4'-diOH essential	R ² = 0.78	[19],[73]
Triterpenoids	Pentacyclic structure	Antifungal dominant	C-3 hydroxylation critical	R ² = 0.71	[74]
Phenolic acids	Carboxyl + phenolic groups	Moderate activity	ortho-diOH increases potency	R ² = 0.82	[75]
Alkaloids	Nitrogen heterocycles	Anti-biofilm	Quaternary N enhances activity	R ² = 0.69	[76]
Tannins	Multiple phenolic units	Enzyme inhibition	Higher MW = ↑ selectivity	R ² = 0.74	[60]

SAR: Structure-Activity Relationship; MW: Molecular Weight; R²: Correlation coefficient

Table 5: Synergistic Interactions Between Euphorbiaceae Extracts and Conventional Antibiotics

Plant Extract	Antibiotic	Target Organism	FIC Index****	Interaction Type	Fold Reduction	Clinical Significance	Reference
<i>E. hirta</i> (MeOH)	Ampicillin	MRSA	0.31	Synergistic	8-fold	Restored sensitivity	[61]
<i>E. milii</i> (EtOH)	Ciprofloxacin	<i>E. coli</i>	0.42	Synergistic	4-fold	Enhanced penetration	[35],[54],[63]
<i>E. tirucalli</i>	Fluconazole	<i>C. albicans</i>	0.28	Synergistic	16-fold	Reduced resistance	[65]
<i>E. pulcherrima</i>	Gentamicin	<i>P. aeruginosa</i>	0.38	Synergistic	6-fold	Biofilm disruption	[62]
<i>E. antiqorum</i>	Vancomycin	<i>E. faecium</i>	0.45	Synergistic	3-fold	VRE treatment	[64]
<i>E. royleana</i>	Tetracycline	<i>S. aureus</i>	0.51	Additive	2-fold	Efflux inhibition	[61]
<i>E. lactea</i>	Ceftriaxone	<i>K. pneumoniae</i>	0.33	Synergistic	12-fold	β-lactamase inhibition	[75]

****FIC Index: Fractional Inhibitory Concentration Index (≤0.5 = Synergistic, 0.5-1.0 = Additive, >1.0 = Antagonistic) VRE: Vancomycin-Resistant Enterococci

CONCLUSION

The Euphorbiaceae family represents a valuable reservoir of antimicrobial compounds with significant therapeutic potential. The combination of broad-spectrum activity, novel mechanisms of action, and synergistic interactions with conventional antimicrobials positions these plants as promising candidates for addressing current antimicrobial resistance challenges. However, successful translation from laboratory findings to clinical applications requires continued research focusing on compound purification, mechanism elucidation, safety assessment, and standardized preparation methods. The integration of traditional knowledge with modern scientific approaches offers a promising pathway for developing next-

generation antimicrobial therapeutics from this remarkable plant family.

Acknowledgments

The authors would like to express their sincere gratitude to the Department of Botany, Patliputra University, for providing the necessary administrative and technical support throughout this study. We also acknowledge the department's contribution in facilitating access to laboratory facilities and materials essential for the experimental work.

Conflict of interest

The authors declared no conflict of interest.

Financial Support

None declared.

ORCID ID

Abhishek Kumar: <https://orcid.org/0000-0002-7231-8507>

Pushpa Kamari: <https://orcid.org/0009-0003-6752-2428>

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HOW TO CITE THIS ARTICLE

Kumari P, Kumar A, Kumar S, Fazal M. Antimicrobial potential of Euphorbiaceae plants: A comprehensive review of bioactive compounds, mechanisms, and therapeutic applications. *J Phytopharmacol* 2025; 14(4):258-266. doi: 10.31254/phyto.2025.14405

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