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Antimicrobial effects of *Euphorbia hirta* against medically significant microorganisms: A narrative review

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Abstract

Euphorbia hirta, commonly known as asthma wood or tawa-tawa, has been widely used as a traditional medicine to treat cough, indigestion, and dengue fever. Recent studies have focused on exploring its antimicrobial properties, positioning *E. hirta* as a potential natural source against medically significant microorganisms. This narrative review analyzed publications exploring the antibacterial, antifungal, and antiviral activities of *E. hirta* in different concentrations and extraction forms. Spanning from 2009 to 2023, the review compiled 39 relevant studies from sources such as Google Scholar and ResearchGate. The results showed that *E. hirta's* antimicrobial activities were linked with quercetin (flavonoid), gallic acid (phenol), and tannins. In terms of antibacterial activity, *E. hirta* demonstrated efficacy against a spectrum of gram-negative and gram-positive bacteria. Methanolic extracts exhibited high efficiency, showcasing its potential in addressing conditions such as urinary tract infections, pneumonia, and infections caused by *Escherichia coli* and *Klebsiella pneumoniae*. Using similar phytochemical properties, *E. hirta* demonstrated substantial inhibition of certain fungal species by changing their cell growth and morphology, showing the highest efficiency of ethanolic leaf extracts. This suggests potential use in treating localized fungal infections. Additionally, the plant exhibited antiviral activity against SARS-CoV-2 and other viruses by inhibiting the main protease (Mpro), with leaf methanolic extracts displaying the greatest potency. Such results revealed the promising qualities of *E. hirta* as a natural solution against a wide array of clinically significant microorganisms. Further studies can, therefore, be undertaken to examine other medicinal properties of *E. hirta* with this article serving as a foundation.

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Introduction

The Institute for Health Metrics and Evaluation highlights the alarming toll of increasing drug-resistant infections with an estimated 1.27 million global deaths since 2019 (Patel *et al.*, 2023). Regions of Sub-Saharan Africa and South Asia particularly bear significant mortality rates linked to drug-resistant infections. However, despite the pressing need for novel antibacterial treatments, the pharmaceutical development landscape, as outlined in the World Health Organization's annual report (2022), constantly falls behind. Only a meager 12 antibiotics have received approval in the past four years, and the majority belongs to established classes with recognized mechanisms of antimicrobial resistance (AMR) (Gigante *et al.*, 2022). This underscores the demand for innovative compounds capable of addressing unmet medical needs and circumventing known mechanisms of drug resistance across a wider spectrum, particularly against antibacterial, antifungal, and antiviral drugs.

Recent years have witnessed a surge in scientific exploration of *Euphorbia hirta's* (Tawa-Tawa) traditional uses, particularly its antimicrobial properties. Multiple studies have delved into its potential as an antibacterial agent, with Elisha *et al.* (2023) conducting a comprehensive bibliometric analysis spanning nearly the past three decades. The predominant research themes during this period have focused on leveraging crude extracts or isolated compounds from *E. hirta* to combat various infections from different clinically significant microorganisms.

E. hirta, frequently referred to as asthma weed, is an herb with medicinal properties in the Kingdom Plantae (Verma, 2017). This plant is a member of the *Magnoliopsida* class, the *Malpighiales* order, and belongs to the family *Euphorbiaceae*. Morpho-anatomical research by De Villa (2017) demonstrated that its roots are like a main taproot, and its stem grows with a single main branch. The leaves are simple, grow in pairs on opposite sides, and are long and slightly serrated, with one side being rounded and the other side coming to a point.

In the Philippines, the conventional relevance of Tawa-Tawa extends beyond its medicinal applications, embodying a cultural connection that is unique to the Filipino context. According to Lam *et al.* (2018), Tawa-Tawa was used traditionally to treat fever in the early days. The study further reported that since the 1980s, *E. hirta* has been used to treat conjunctivitis, cough, diabetes mellitus, break-bone fever, malaria, gastritis, and diarrhea.

Currently, a study by Tran *et al.* (2020) has demonstrated that the secondary metabolites of *E. hirta* could be of potential use as an antibacterial agent. Perera *et al.* (2018), on the other hand, indicated that the plant has antiviral characteristics and platelet-increasing properties that make it a potential treatment for viral infections. Moreover, Ballentes and Pradera (2019) conducted tests on *E. hirta* leaf extracts against medically significant fungi yield promising results against fungal infections. With this ever-evolving expansion of knowledge regarding the therapeutic potential of *E. hirta,* the need to comprehensively investigate its multi-faceted capacity as an antibacterial, antifungal, and antiviral agent is revealed to be a principal concern.

This study encompasses three primary objectives. Firstly, it endeavors to conduct a comprehensive literature review elucidating *E. hirta's* antimicrobial properties against bacteria, fungi, and viruses. This review serves as a foundational exploration to discern the mechanisms through which *E. hirta's* bioactivities interact with these medically significant microorganisms. Secondly, the study aims to assess and compare the efficacy of *E. hirta* as an antimicrobial agent. This involves a synthesis of available data, scrutinizing the inhibitory effects across varying concentrations and forms of extraction. Thirdly, the research focuses on delineating *E. hirta's* antimicrobial effects against a spectrum of potential diseases and other pathogenic conditions. The goal is to discover insights and medical significance that could prove invaluable in navigating the dynamic landscape of clinical settings. This exploration aims to identify the practical applications of *E. hirta* in addressing a diverse range

of health challenges in the ever-evolving field of medicine and public health. By investigating potential nuances in efficacy across diverse microbial pathogens and determining any relationship with specific microbial characteristics, the study contributes to a nuanced understanding of how *E. hirta* can be tailored for various medical applications.

Academic institutions stand to benefit from its comprehensive insights, as the research serves as a valuable resource for students and educators interested in traditional medicine, microbiology, or pharmaceutical sciences. Furthermore, its relevance extends to medical technology education, where the study enhances the knowledge base of aspiring medical technologists by providing evidence-based information on *E. hirta's* antimicrobial efficacy and variations across different microorganisms and extraction forms. This direct application in education underscores the practical implications of the research for future healthcare professionals. The seamless connection between academic institutions, medical technology education and practice, health and community research, the pharmaceutical industry, public health, and future research underscores the interdisciplinary significance of this comprehensive examination of *E. hirta's* antimicrobial efficacy.

Materials and methods

Study design

This study employed a narrative approach to provide a comprehensive review of existing literature, emphasizing a thorough examination of various studies. The focal point of the study resided in a qualitative investigation utilizing descriptive analysis methods. The methodology started with a systematic literature search, leveraging reputable databases and specific keywords through inclusion-exclusion criteria. To mitigate bias through quality assessment, researchers thoroughly chose and extracted studies based on their relevance to the research topic, starting with a comprehensive screening of titles, abstracts, and then full text. The Critical Appraisal Skills Programme (CASP) Systematic Review Checklist was used to serve as a basis for appraising the existing literature for its results, validity, and significance. Individual reviewers were assigned to check for the accuracy of the obtained literature and provide a corresponding score for each criterion as deemed appropriate. Strict adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was maintained to ensure systematic reporting.

Inclusion and exclusion criteria

The researchers adhered to strict inclusion and exclusion criteria to focus on the antimicrobial activity of *E. hirta*. The inclusion criteria for this research incorporated only the antimicrobial properties of *E. hirta* without considering other species under the genus *Euphorbia*. Utilizing reputable sources such as Google Scholar and ResearchGate, the researchers aimed to gather diverse and relevant literature from journals that are Scopus-indexed with complete authors, DOI, and full-text articles. The criteria for exclusion would notably involve disregarding journal articles published by predatory publishers, which pertains to those with insufficient editorial standards and peer review. Additionally, this study only included open access journal articles that were published in the English language between 2009 and 2023 to maintain focus on recent and relevant studies. Incomplete journals were disregarded.

Data collection

Following the PRISMA protocol, the researchers conducted a literature search in Google Scholar and ResearchGate using the combination of words "*Euphorbia hirta*," "*E. hirta*," "antibacterial activity," "antiviral activity," "antifungal activity," "antimicrobial activity," and "antimicrobial effects." The researchers obtained articles that are aligned with the aim and objectives of the study. This involved various parameters such as (1) Author and Year of Publication, (2) Bioactivity, (3) Parts Used, (4) Concentrations Administered, (5) Extraction Forms, (6) Test Organisms, (7) Inhibitory Effects, and (8) Medical Significance. The gathered articles were stored in a secured digital archive (Google Docs), to

ensure proper organization and easy access for subsequent stages of the research. All the articles were tabulated and arranged alphabetically.

Data analysis

The data analysis in this narrative review adhered to the PRISMA guidelines—a 27-item checklist used to evaluate different pieces of literature collected. Following the checklist, the data gathered were synthesized to provide a comprehensive overview of the antimicrobial effects of *E. hirta* against medically significant microorganisms. The researchers used a PRISMA flow diagram to exhibit the step-by-step screening process of study selection and inclusion. The diagram is composed of the number of articles and publications collected, included, and excluded, as well as the reasons for the inclusion and exclusion at each stage. Throughout the collection and selection process, blind testing was utilized by independent reviewers, ensuring an unbiased evaluation as they were kept uninformed about specific details or characteristics associated with the studies under consideration. Cross-checking mechanisms were implemented to ensure consistency and accuracy in the screening process. The literature search involved each of the five authors independently conducting searches across databases using the specified search terms. Two independent authors conducted the initial and second rounds of screening based on title and abstract. The final screening was done by two independent authors based on full-text articles to ensure adherence to eligibility criteria. In instances of conflicts regarding the inclusion of an article, another author was involved for further consensus.

Ethical consideration

This study exclusively relied on publicly accessible studies, prioritizing reliable sources. The involvement of the University Research Center's ethics review committee affirmed adherence to ethical standards throughout the study, reinforcing the credibility of the narrative review.

Results and Discussion

Among the initial pool of 50 articles identified for potential inclusion in this narrative review, only 39 studies met the predetermined eligibility criteria (Fig. 1).

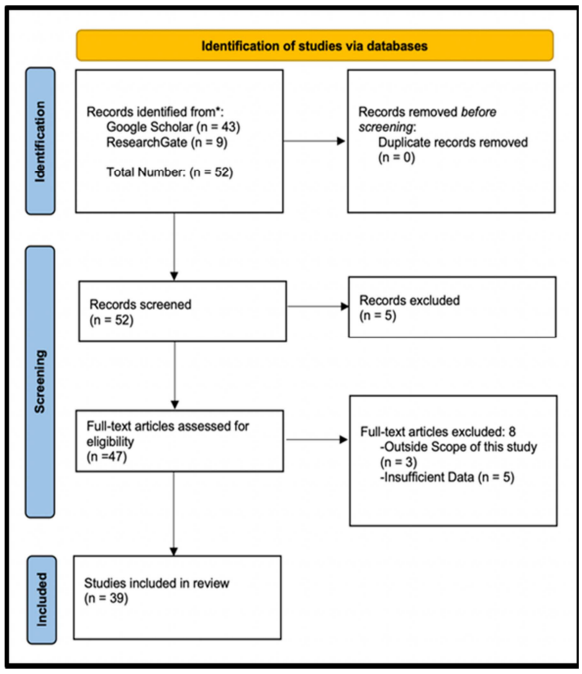

Fig. 1. Study selection flowchart

Phytochemical analysis of E. hirta

Ghosh *et al.* (2020) studied the phytochemical composition and medicinal properties of five wild weed species, focusing on antioxidant and antibacterial activities. The investigation generally identified polyphenols, flavonoids, and tannins, with specific compounds like quercetin and gallic acid contributing to antimicrobial properties. The research enhances our understanding of the antibacterial potential of plant extracts, particularly *E. hirta*, against medically significant microorganisms. In contrast, Mekam *et al.* (2019) explored the phytochemicals in *E. hirta*, finding ethanol extracts with strong antioxidant and antifungal properties. This implies that *E. hirta* may contain phenolic compounds effective against a range of microbes, expanding its applications beyond fungal infections to include therapeutically significant bacteria.

In the research conducted by Basma *et al.* (2011), it was discovered that *E. hirta* possesses reduced sugars, alkaloids, terpenoids, tannins, steroids, flavonoids, and phenolic compounds. Additionally, Asha *et al.* (2015) and Ghosh *et al.* (2019) expanded the list, indicating the existence of carbohydrate, amino acids, proteins, glycosides, coumarin, saponin, volatile oils, anthraquinone, gums, and mucilage in the medicinal plant.

Table 1. Phytochemical analysis of *E. hirta*

Author (Year)	Phytochemical content	Bioactivity
Ghosh *et al.* (2020)	Polyphenol	Antimicrobial
	Flavonoid	
	Tannin	
Mekam *et al.* (2019)	Phenolic Compound	Antioxidant and Antifungal
Karki *et al.* (2020)	Flavonoid	Antioxidant, Anti-inflammatory, Anti-cancer, Anti-diabetic
	Alkaloid	Antimicrobial and Anti-tumor
Kiệm *et al.* (2020)	Saponin	Cytotoxic and Anti-ulcer

Table 2. Antimicrobial mechanism of action of *E. hirta*

Author (Year)	Compound	Mechanism
Rasooly *et. al* (2020)	Gallic Acid	Alters microbial membrane structure; Disrupts metabolism; Inhibits biofilm formation
Yang *et. al* (2020)	Quercetin	Inhibits biofilm formation; Disrupts quorum sensing pathways
Shi *et. al* (2021)	$C_{28}H_{18}O_{15}$	Mutilates membrane; Inhibits release of virulence factor; Biofilm suppression

Table 3. *E. hirta's* phytochemical analysis and antibacterial mechanism of action

Author (Year)	Phytochemical Content	Specific Mode of Action
Patel *et al.* (2014)	Alkaloids, Tannins, Flavonoids	Not specified
Kader *et al.* (2013)	Alkaloids, Phenols, Tannins	Disrupt the cell wall of bacteria
Tran *et al.* (2020)	Flavonoids, Terpenoids, Phenols, Essential Oils	Not specified

The plant contains a significant quantity of flavonoids, which contribute to biochemical activities and pharmacological impacts, including anti-inflammatory, anti-cancer, anti-diabetic, immune-stimulating effects, and antioxidant properties, as stated by Karki *et al.* (2020). The study also highlighted that the presence of flavonoids can aid in antimalarial activity. On the other hand, the plant extract's saponins are documented to exhibit cytotoxic and anti-ulcer properties; this also contains emulsifying properties responsible for acting as a chemical barrier against potential pathogens (Kiệm *et al.,* 2009). Meanwhile, the study of Karki *et al.* (2020) states that antimicrobial and antitumor actions can be attributed to alkaloids (Table 1).

Antimicrobial mechanism of action

E. hirta is known to contain various medically significant phytochemicals that makes it a well-known herbal alternative for some diseases. Specifically, various studies were able to put an emphasize on its well-established antimicrobial properties attributed to its key components: gallic acid (phenols), quercetin (flavonoid), and a newly discovered phenolic substance with the chemical formula $C_{28}H_{18}O_{15}$ (Singh and Kumar, 2013; Enerva *et al.*, 2015). According to the study of Rasooly *et al.*, (2020), gallic acid's general antimicrobial mechanism includes altering of the microorganism's membrane structure, disrupting metabolism, and preventing biofilm formation. Quercetin, on the other hand, similarly inhibits biofilm formation and disrupts quorum sensing pathways, impeding microbial adhesion and formation (Yang *et al.,* 2020). While the newly identified phenolic substance, $C_{28}H_{18}O_{15}$, shares characteristics with known phenolic compounds and is likely to hinder microbial growth through its mechanisms such as mutilation of membrane, inhibition of virulence factor release, and also suppression of biofilm formation just like the other two (Shi *et al.,* 2021) (Table 2). These findings collectively suggest a multifaceted antimicrobial mechanism within *E. hirta*'s components.

Antibacterial properties

E. hirta has attracted considerable interest due to its perceived potential as an antibacterial agent. According to a study by Patel *et al.* (2014), it was discovered that the extracts derived from *E. hirta* consist of compounds like alkaloids, tannins, and flavonoids, which possess the ability to impede the growth of diverse microorganisms (Table 3).

Table 4. Inhibitory effects of *E. hirta*'s antibacterial properties based on various concentrations and extraction

Author (Year)	Method	Parts Used	Extracting Solvent	Concentration Administered	Target Bacteria	Inhibitory Effects
Patel (2014)	Kirby-Bauer Diffusion Disc Method	Young branches with leaves and inflorescence	Acetone	(12.5µg/µl) (25µg/µl)	*K. pneumoniae* *E. coli,* *P. aeruginosa,* *P. vulgaris*	Excellent Moderate
			Methanol	(12.5µg/µl) (25µg/µl) (50µg/µl)	*K. pneumoniae,* *P. aeruginosa* *E. coli* *P. vulgaris*	Excellent Good Moderate
			Aqueous	(12.5µg/µl) (25µg/µl) (50µg/µl) (100µg/µl)	*K. pneumoniae* *P. aeruginosa* *E. coli* *P. vulgaris*	Excellent Good Moderate Weak
			Petroleum Ether	(25µg/µl) (50µg/µl)	*K. pneumoniae* *P. vulgaris*	Good Moderate
Kader *et al.* (2013)	Agar Well Diffusion Method	Whole plant (*W*), Flowers (F), Stems (*S*), Leaves (*L*), and Roots (*R*)	Acetone	1000 mg/mL		W F S L R
					B. cereus	s s s s s
					B. subtilis	s s s s s
					E. faecalis	s s s s s
					S. aureus	s s s s s
					S. epidermidis	s s s s s
					K. pneumoniae	r r r s r
					S. typhimurium	r r r r r
					S. marcescens	r s r s r
					S. dysentriae	s s s s s
					S. sonnei	s s s s s
Tran *et al.* (2020)	Disc Diffusion Method	Not Specified	Absolute Methanol (Me)	(400 mg/mL)	*V. cholearea*	Inhibition Zone Observed
			Petroleum Ether (PE)	(200 mg/mL)	*B. subtilis*	Inhibition Zone Observed
			Chloroform (Ch)	(200 mg/mL) (400 mg/mL)	*V. cholearea* *B. subtilis*	Inhibition Zone Observed
			Ethyl Acetate (EA)	(200 mg/mL) (400 mg/mL)	*S. typhi,* *V. cholearea* *S. preumoniae,* *S. flexneri*	Inhibition Zone Observed
			Butanol (Bu)	(400 mg/mL)	*V. cholearea*	Inhibition Zone Observed
Edrees (2019)	Agar Well Diffusion Method	Leaves and Stems	Aqueous Methanolic	(50µL) (100µL) (150µL)	*E. coli* *P. mirabilis* *P. aeruginosa* *S. aureus*	Susceptible to both Aqueous and Methanolic extracts at different concentration

(s) Susceptible; (r) Resistant

Similarly, in another investigation by Tran *et al.* (2020), it was noted that *E. hirta* possesses an array of secondary metabolites, such as flavonoids, terpenoids, essential oils, phenols, and others. However, there is a variance in their findings concerning the targeted bacteria, as this study showcased the antibacterial effectiveness of *E. hirta* against various bacterial strains, including *Shigella species, Escherichia coli, Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. On the other hand, Kader *et al.* (2013) emphasized the intrinsic resistance to *E. hirta* extracts of gram-negative bacteria and highlighted the effectiveness of crude leaf and whole plant extracts against diverse bacterial strains. The crude leaves extract demonstrates the highest antibacterial activity, attributed to the abundance of phytochemicals such as alkaloids, phenols, and tannins. Each study employed different extraction methods, evaluated various parts of the plant and

highlighted the diverse biological activities of *E. hirta* extracts. As emphasized in these studies, *E. hirta* exhibits antibacterial properties attributed to compounds like alkaloids, tannins, flavonoids, and more showcasing its effectiveness against a range of microorganisms, specifically bacteria.

Inhibitory effects

Patel *et al.* (2014) mentioned that methanol, acetone, aqueous, and petroleum ether extracts of *E. hirta* exhibited effects of inhibition against the gram-negative bacteria used. The zone of inhibition indicated the effectiveness of *E. hirta* extracts, with variations observed among various solvents and bacterial strains. Complementing this study, Tran *et al.* (2020) also used organic solvents for *E. hirta* extraction which include butanol (Bu), methanol (Me), chloroform (Ch), petroleum ether (PE), and ethyl acetate (EA). The study revealed EH-EA (*E. hirta*-ethyl acetate) extract's significant inhibitory effects. Edrees (2019), on the other hand, delved into *E. hirta's* capacity to combat multidrug-resistant bacteria from surgical wounds, particularly *Proteus mirabilis*. The antibacterial activity was assessed against *P. mirabilis, P. aeruginosa, E. coli,* and *S. aureus*. The results display that the extracts, both aqueous and methanolic, exhibited significant effects of inhibitory on most bacterial species, with a particular emphasis on their efficacy against *P. mirabilis*. Generally, gram-negative bacteria exhibit higher resistance to *E. hirta* extracts in contrast to gram-positive bacteria. This resistance is attributed to its outer membrane, which provides a barrier to protect the cell wall and restrict the diffusion of hydrophobic compounds, making them less susceptible (Kader *et al*, 2013).

Furthermore, Edrees (2019) revealed that the *E. hirta*'s methanolic extracts were found to be more effective than the aqueous extracts, especially at a 150 µL concentration (Table 4). Nevertheless, it is observed that ciprofloxacin, an antibiotic, exhibited greater inhibitory efficacy compared to other antibiotics employed in the study. In contrast, the extracts from *E. hirta* demonstrated heightened effectiveness compared to antibiotics against the majority of bacterial species, particularly at a 150 µL concentration. The results of this study underscore the influence of extraction methods in harnessing *E. hirta*'s antibacterial capacity. Moreover, Patel (2014) showed that the extracts, obtained through various solvents (acetone, methanol, aqueous, petroleum ether), displayed different levels of inhibitory effect against bacteria such as *Klebsiella pneumoniae, E. coli, P. vulgaris, and P. aeruginosa*. Specifically, the acetone extract showcased outstanding antibacterial activity against *K. pneumoniae*, whereas the methanol extract showed excellent activity against *K. pneumoniae* and *P. aeruginosa,* and the aqueous extract demonstrated excellent activity towards *K. pneumoniae*. However, aqueous extract only yielded good activity against *P. aeruginosa* and *E. coli*. The petroleum ether extract, on the other hand, demonstrated good activity against *K. pneumoniae* and moderate activity against *P. vulgaris*. The findings indicated that the inhibitory effects varied based on both the type of extraction solvent and the concentration of the extracts. Tran *et al.* (2020) complemented this study as it examined the effectiveness of *E. hirta* extracts against clinically significant bacterial strains, particularly highlighting the significance of EH-EA extract's inhibitory effects. The findings revealed that EH-Ch and EH-EA extracts showed heightened antibacterial inhibition effects in comparison to other extracts, with EH-EA demonstrating the most potent antibacterial activity. However, it was observed that all extracts displayed minimal inhibitory effect towards *E. Coli, P. aeruginosa, and S. aureus* at various concentrations.

The diverse studies highlight the significant inhibitory effects of *E. hirta* extracts against gram-positive and gram-negative bacteria, underscoring the importance of solvent selection and extraction methods. Despite differences in bacterial strains and solvents, these combined results underscore the potential of *E. hirta* as a valuable reservoir of antibacterial agents, encouraging additional exploration for therapeutic purposes.

Table 5. *E. hirta's* therapeutic impact against bacterial pathogens

Author (Year)	Target bacteria	Medical significance
Patel (2014)	gram-negative bacteria, including *E. coli, P. aeruginosa, P. vulgaris* and *K. pneumoniae,*	Significant antibacterial activities against pathogens associated with urinary tract infections (UTIs)
Tran *et al* (2020)	Gram-negative bacteria, including *V. cholearea, S. typhi, S. flexneri* and *E. coli* Gram-positive bacteria, including *B. subtilis* and *S. preumoniae*	Address a spectrum of pathogens associated with severe conditions such as diarrhea, acute diarrhea, and pneumonia; potential in managing diverse strains of E. coli associated with various diseases
Kader *et al.* (2013)	*B. cereus, B. subtilis, E. faecalis, S. aureus, S. epidermidis, K. pneumoniae, S. typhimurium, S. marcescens, S. dysentriae, S. sonnei*	Support for traditional use in treating conditions like athlete's foot, dysentery, enteritis, and skin conditions

Table 6. *E. hirta's* phytochemical analysis and antifungal mechanism of action

Author (Year)	Phytochemical content	Specific mode of action
Ballentes and Pradera (2019)	Saponins, tannins, flavonoids and alkaloids	Not specified
Rajeh *et al.* (2010)	Not specified	Not specified
Rao *et al.* (2010)	Saponins, flavonoids alkaloids, tannins, proteins, glycosides and sterols	Not specified
Kumar *et al.* (2010)	Flavonoids, alkanes, amino acids and alkaloids	Not specified
Gayathri and Ramesh (2013)	Not Specified	Disrupt fungal cell membranes

Table 7. Inhibitory effects of *E. hirta's* antifungal properties based on various concentration and extraction

Author (Year)	Method	Parts Used	Extracting Solvent	Concentration Administered	Target Fungi	Inhibitory Effects
Ballentes and Pradera (2019)	Agar Well Diffusion Technique	Leaves	Crude Aqueous Extract (CAE) and Crude Ethanolic Extract (CEE)	(25%) (50%) (75%) (100%)	*C. albicans, M. pachydermatis* and *T. mentagrophytes*	Inhibition zone observed
Gayathri and Ramesh (2013)	Microtiter Plate Assay	Whole plant	Ethyl acetate	100 mL	*A. flavus*	Great leakage
Rajeh *et al.* (2010)	Disc Diffusion Method and Broth Dilution	Whole plant (W), Flowers (F), Stems (s), Leaves (L), and Roots (R)	Methanol	400 mL	*C. albicans*	Inhibition zone observed

Table 8. *E. hirta's* therapeutic impact against fungal pathogens

Author (Year)	Target fungi	Medical significance
Ballentes and Pradera (2019)	*T. mentagrophytes, C. Albicans,* and *M. pachydermatis*	Can help people and animals with dermatophytosis and yeast infections
Khan *et al.* (2011)	*A. flavus*	Address sinus and ocular problems to skin, wound, and bone infections, typically following trauma or exposure.

Table 9. *E. hirta's* phytochemical analysis and antiviral mechanism of action

Author (Year)	Phytochemical content	Specific mode of action
Cayona and Creencia (2021)	Flavonoids Coumarin and derivatives Depsides and Depsinones Tannins	Not specified
Gyuris *et al.* (2009)	Tannins	Not specified
Tayone *et al.* (2020)	Flavonoids and triterpenes	Not specified
Siva Ganesh *et al.* (2015)	Flavonoids	Not specified

Medical significance

In an investigation by Patel (2014), the antibacterial effectiveness of *E. hirta's* extract against gram-negative bacteria was evaluated using the Kirby-Bauer Disc Diffusion Method. The findings demonstrated noteworthy antibacterial activities against various gram-negative microorganisms, including *E. coli, P. aeruginosa, P. vulgaris,* and *K. pneumoniae*. These bacteria are commonly associated with urinary tract infections (UTIs) (Table 5).

On the other hand, Tran *et al.* (2020) investigated *E. hirta* extracts as an antibacterial agent against various bacteria, including gram-positive and gram-negative strains, utilizing the agar disc diffusion method. The selected bacterial strains are linked to severe conditions such as pneumonia, acute diarrhea, and diarrhea, which are characterized by elevated mortality rates. *E. coli* was specifically mentioned as a diverse group of bacteria with roles in human life, such as immune stimulation and metabolic functions. However, certain strains of *E. coli* can lead to diseases like urinary tract infections and meningitis. This study underscores its potential in addressing a spectrum of pathogens associated with diseases like diarrhea and pneumonia.

In the findings by Kader *et al.* (2013), the presence of various phytochemicals, except for phlobatannins, contributed to the inhibitory results, supporting the traditional use of *E. hirta* in treating conditions such as enteritis, dysentery, athlete's foot, and skin conditions. The extracts demonstrated bactericidal effects against the tested bacteria, with susceptibility observed in gram-positive bacteria, particularly *Staphylococcus epidermidis*.

Notably, these collective findings underscore the potential of *E. hirta* as a valuable natural resource for developing antimicrobial agents with broad applicability in combating bacterial infections as the significant antibacterial efficacy of *E. hirta* extracts were highlighted.

Antifungal properties

The investigation of *E. hirta*, a medicinal plant known for its therapeutic properties, has garnered attention in various studies due to its potential in combating fungal infections. Ballentes and Pradera (2019) conducted tests on *E. hirta* ethanolic extracts and leaf crude aqueous and against *Malassezia pachydermatis, Candida albicans, and Trichophyton mentagrophytes,* yielding promising results against fungal infection because of alkaloids, tannins, saponins, and flavonoids. In a separate study by Rao *et al.* (2010), they studied the antifungal effects of ethanol extract from *E. hirta* leaves across different seasons, observing significant efficacy against *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger,* and *Rhizopus oryzae*, notably between mid-August and December, corresponding to winter. Additionally, Kumar *et al.* (2010) states the ethanolic extract of *E. hirta* displayed antifungal activity against *Phoma caricae-papayae, Colletotrichum capsici, A. niger, Botryodiplodia theobromae, and Fusarium pallidoroseum* using the paper disc diffusion technique. Moreover, Gayathri and Ramesh (2013) studied the plant's mode of action against *A. flavus* inflorescence, emphasizing its ability to disturb fungal cell membranes, particularly in relation to the release of cellular proteins. Despite the promising results conducted by Kumar *et al.* (2010), Ballentes and Pradera (2019), Rao *et al.* (2010), and Gayathri and Ramesh (2013), it is essential to acknowledge the caution raised by Rajeh *et al.* (2010) regarding excessive consumption and observed toxicity, adding a layer of complexity to its therapeutic use. Collectively, the studies on *E. hirta*'s antifungal attributes, from its bioactive compounds to seasonal variations in efficacy and mode of action against fungal cells, express its potential as a natural remedy against fungal infections (Table 6).

Inhibitory effects

Ballentes and Pradera (2019) investigated the effectiveness of varying concentrations of Tawa-tawa crude ethanolic extract (CEE) and crude aqueous extract (CAE) against different test organisms, observing increased inhibition as concentrations rose from 25% to 100%. The 0.2 mg/ml Tioconazole which serves as the positive control, showed the most extensive inhibitory effect across all organisms.

However, when compared to Tawa-tawa extracts, especially in lower concentrations, it displayed significantly stronger inhibition against certain organisms like *T. mentagrophytes and C. albicans*. For *T. mentagrophytes*, the positive control had a notably higher inhibitory effect than lower concentrations of Tawa-tawa extracts, both in CEE and CAE.

While CEE at higher concentrations approached the efficacy of the positive control, CAE exhibited less effectiveness against this organism in lower concentrations. Concerning *C. albicans*, all concentrations of Tawa-tawa extracts showed effectiveness, but the positive control displayed significantly greater inhibition than the lower concentrations of the extracts. *M. pachydermatis* was found to be most sensitive to both CAE and CEE among the organisms tested. Even though the positive control had the highest inhibition, especially in CAE, at times, the effectiveness of the extracts at higher concentrations approached the efficacy of the positive control.

Additionally, in a study conducted by Gayathri and Ramesh (2013), they tested *E. hirta's* ethyl acetate extract, Fluconazole (Drug 1), and Amphotericin B (Drug 2) against *A. flavus* strains. Their findings demonstrated changes in fungal growth and structure, suggesting that *E. hirta* possesses the capability to potentially hinder the growth of *A. flavus*.

While both Ballentes and Pradera (2019) as well as Gayathri and Ramesh (2013) explored the efficacy of Tawa-tawa's ethanolic extract, showing significant results on various organisms.

On a different note, Rajeh *et al.* (2010) utilized methanol extraction. The investigation involved extracting 100 grams of powdered parts (leaves, stems, flowers, roots) using methanol (400 mL) through maceration for 14 days with regular stirring. Their results exhibited substantial antibacterial and antifungal activity, indicated by inhibition zones ranging from 16–29 mm against tested microbes.

The leaf extract notably exhibited fungicidal activity against *C. albicans*, leading to a substantial decrease in cell growth without any observed recovery.

Scanning Electron Microscope (SEM) images supported these findings, showing significant alterations in *C. albicans* cells treated with the leaf extract, including changes in surface morphology, invaginations, convolutions, and cell wall cracks, indicating severe damage and loss of metabolic function in the cells (Table 7).

Medical significance

The study of Ballentes and Pradera (2019) highlighted the strong antifungal activities of *E. hirta's* extract against *M. pachydermatis*, *T. mentagrophytes, and C. albicans*. In small animals globally, yeast infections and dermatophytosis stand as the most prevalent fungal infections. Dermatophytes, notably *T. mentagrophytes*, primarily affect keratinized tissues, known as ringworm, with a zoonotic nature often transmitted between asymptomatic pets and their owners. *C.albicans* inhabits mucous membranes in various body areas such as vagina, while *M. pachydermatis* resides on skin, ears, and other regions in dogs and cats. These are opportunistic pathogens, causing localized infections that, in immunocompromised individuals, may progress to systemic mycotic infections.

Moreover, Khan *et al.* (2011) utilized the agar tube dilution technique to evaluate *E. hirta's* methanolic extract for antifungal effects. Their findings indicated significant efficacy against *A. flavus*, known for causing a range of conditions from sinus and ocular problems to skin, wound, and bone infections, typically following trauma or exposure. These studies collectively demonstrate the promising antifungal potential of *E. hirta's* extract against various pathogenic fungi, suggesting its possible application in combating fungal infections (Table 8).

Antiviral properties

E. hirta is renowned for its numerous antimicrobial attributes, with a notable emphasis on its efficacy in addressing retroviral infections.

Cayona and Creencia (2021) examined the bioactive compounds of *E. hirta,* assessing its ability to impede the main protease (Mpro) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the key regulator in viral replication. The research unveiled 298 distinct phytochemical properties of *E. hirta*. Utilizing molecular docking, a virtual screening disclosed 12 potential inhibitors targeting SARS-CoV-2 Mpro and other viruses.

Additionally, Gyuris *et al.* (2009) conducted an evaluation of *E. hirta's* antiretroviral potential. This investigation employed in vitro testing on the MT4 human T lymphocyte cell line, with the assessment of cytotoxicity via the MTT cell proliferation assay. They found dose-dependent inhibition of reverse transcriptase (RT) activity for Human Immunodeficiency Virus Type 1 and 2 (HIV-1 & HIV-2) and Simian Immunodeficiency Virus strain mac251 (SIVmac251). Moreover, they compared the antiretroviral effects of aqueous and 50% methanolic extracts, with the latter proving more potent, and identified tannins as potential contributors to this activity. In a separate study, Tayone *et al.* (2020) investigated *E. hirta's* chemical composition, revealing known flavonoids and triterpenes, and examined their effect on the Japanese encephalitis virus. Notably, myricitrin exhibited significant inhibition of viral particle production. Furthermore, a study conducted by Siva Ganesh *et al.* (2015) delved into the chemical composition of *E. hirta*, using docking studies focusing on its constituents, notably quercetin—a flavonoid. The investigation revealed favorable docking scores of quercetin with proteins associated with dengue, Human Immunodeficiency Virus (HIV), and influenza. These scores suggest the potential efficacy of quercetin as an agent effective against the dengue virus. However, Perera *et al.* (2018) emphasized the necessity of validating the data from theoretical investigations on anti-dengue properties conducting assays on pure compounds to ensure data accuracy (Table 9).

Inhibitory effects

Perera *et al.* (2018) conducted a study on the ethanol extract of *E. hirta* in vitro. *E. hirta* revealed a positive result caused by dengue virus serotype 1 and 2. It exhibited an 85% inhibition of plaque on serotype 1 (DENV-1) and a 34.7% inhibition of serotype 2 (DENV-2). In a study by Garber *et al.* (2021) evidenced the antiviral capacity of *E. hirta* by using an extract from its leaves. The extract exhibited significant antiviral activity against HSV-1. This effect was observed through in vitro experimentation involving Vero cells and HeLa cells obtained from *E. hirta*. Moreover, *E. hirta* has demonstrated antiviral capabilities against dengue. In a research conducted by Beressa *et al.* (2021), it revealed that *E. hirta*, when utilized in its entirety, possesses antiviral properties against poliovirus, exhibiting a reduction factor of 10^5. Furthermore, the same study found that *E. hirta* demonstrated antiviral effects against Coxsackie virus (reduction factor of 10^3) and Herpes simplex virus (HSV) (reduction factor of 10^3). Ogbole *et al.* (2021) investigated the antiviral potential of *E. hirta* through methanol extraction from its leaves. The extract derived from *E. hirta* exhibited a noteworthy antiviral efficacy against various non-polio enterovirus species C. It is crucial to note, however, that the study was designed with a prophylactic orientation, aiming to hinder the virus from infecting other cells, rather than possessing therapeutic properties (Table 10).

Medical significance

A study by De Guzman, *et al.* (2016), conducted ethnopharmacological investigation within indigenous communities in Pangasinan, exploring the application of *E. hirta* as a treatment for the dengue virus. The survey revealed that the majority of respondents, particularly females aged 60-80 years, were aware of *E. hirta*'s effectiveness in treating dengue. People commonly use *E. hirta* by making decoctions from its leaves and barks. In addition, Perera *et al.* (2018) studied the platelet augmentation of *E. hirta*. A clinical study involved dengue patients—with two different age groups: 14-25 and 30-55. Within 24 hours, oral administration of *E.hirta* herbal water resulted in elevated platelet and total leukocyte counts. Notably, the older age group exhibited a noteworthy increase in platelet count, whereas the younger age group did not show a

significant rise compared to the control group. This indicates a potential age-related difference in *E. hirta*'s efficacy in increasing platelet counts among dengue patients (Table 11).

Interpretation of results

The emphasis on bioactive compounds revealed few similarities in each domain, with (1) antibacterial activity tied to alkaloids, phenols, and tannins, (2) antifungal properties associated with saponins, tannins, flavonoids, and alkaloids, and (3) antiviral effects linked to diverse phytochemicals, especially flavonoids and triterpenes. *E. hirta* exerted its antimicrobial effects through diverse modes of action across these medically significant microorganisms. In its antibacterial role, the disruption of bacterial growth was a key mechanism attributed to bioactive compounds like alkaloids, phenols, and tannins. Regarding antifungal properties, studies exhibited the plant's mode of action against fungal cells, showcasing its capacity to disrupt fungal cell membranes while inducing the release of cellular proteins. In the antiviral domain, *E. hirta* demonstrated a multifaceted mode of action, encompassing the inhibition of the main protease of various viruses. While no explicit seasonal variations were noted in antibacterial and antiviral properties, antifungal efficacy exhibited a temporal aspect, particularly between mid-August and December. Furthermore, caution was warranted in the antifungal domain due to observed toxicity, particularly concerning *Candida* infections. Employed assay techniques included the paper disc diffusion technique for antibacterial and antifungal assessments, while antiviral activity was evaluated through molecular docking and in vitro tests on cell lines. These comprehensive characteristics highlighted the multifaceted nature of *E. hirta*'s antimicrobial potential providing a foundation for its exploration as a natural remedy against a wide spectrum of infectious agents.

A comprehensive exploration of *E. hirta*'s inhibitory effects among various medically significant microorganisms unveiled intriguing patterns of both convergence and divergence. A shared theme across the three domains was the concentration-dependent relationship governing the inhibitory effects of *E. hirta* extracts. Higher concentrations consistently translated to more potent activity against bacteria, fungi, and viruses, establishing a dose-dependent dynamic. However, nuanced disparities emerged in the selection of test organisms and methodologies. The antibacterial domain meticulously dissected the impact on both gram-negative and gram-positive bacteria, while the antifungal domain scrutinized the effectiveness against a diverse array of fungi. In parallel, the antiviral domain explored the inhibitory effects on specific viruses such as dengue, polio, Coxsackie, and herpes simplex. Additionally, the antibacterial analysis emphasized the influential role of different solvents (acetone, methanol, aqueous, petroleum ether) and extraction methods (utilizing organic solvents like methanol, petroleum ether, chloroform, ethyl acetate, and butanol) on inhibitory effects. In contrast, the antifungal and antiviral investigations, while acknowledging concentration variations, did not underscore solvent nuances as prominently. The microbial landscape was further navigated through discussions of resistance and sensitivity. The antibacterial discourse elucidated the general resistance of gram-negative bacteria compared to their gram-positive counterparts, while the antifungal narrative accentuated the varying sensitivity among different fungal organisms to distinct concentrations of *E. hirta* extracts. Remarkably, the antiviral domain, while not explicitly delving into microbial resistance, reinforced the inhibitory effects against specific viruses at varying concentrations. Furthermore, the methodologies employed for assessment exhibited divergence, with the antibacterial domain relying on the zone of inhibition measured in millimeters, the antifungal domain assessing inhibition against test organisms, and the antiviral domain utilizing percentage inhibition or reduction factors against specific viruses. These intricate differences and commonalities collectively exhibited the multifaceted nature of *E. hirta*'s impact on diverse microorganisms, suggesting a spectrum of mechanisms at play against bacteria, fungi, and viruses.

Table 10. Inhibitory effects of *E. hirta's* antiviral properties based on various concentrations and extraction

Author (Year)	Method	Parts Used	Concentration Administered	Extracting Solvent	Target Viruses	Inhibitory Effects
Perera *et al.* (2018)	Anti-dengue assay, Thin layer chromatography	Whole plant	(12.5 µg/µl) (25 µg/µl) (50 µg/µl) (100µg/µl)	Ethyl acetate	Dengue virus serotype 1 & 2	Capable of neutralizing the virus
Beressa *et al.* (2021)	*not specified*	Whole plant	Not specified	Not specified	Poliovirus	Has a reduction factor of 10^5
	not specified	Whole plant	Not specified	Not specified	Coxsackie virus, Herpes simplex virus	Has a reduction factor of 10^3
Garber *et al.* (2021)	In vitro	Leaf	Not specified	Ethanol	HSV-1 Dengue virus	Not specified
Ogbole *et al.* (2021)	In vitro	Leaf	Not specified	Methanol	Coxsackievirus A13, Coxsackievirus A20, Enterovirus C99	Not specified

Table 11. *E. hirta's* therapeutic impact against viral pathogens

Author (Year)	Target viruses	Medical Significance
De Guzman *et al.* (2016)	Dengue virus	Can be used as a supportive treatment for dengue
Perera *et al.* (2018)	Dengue virus	Can be used as a supportive treatment for dengue to alleviate flu-like symptoms and increase platelet count

The research on the medical significance of *E. hirta*'s antimicrobial effects across antibacterial, antifungal, and antiviral domains also revealed both striking similarities and notable differences. Shared characteristics included the acknowledgment of *E. hirta*'s holistic antimicrobial efficacy against bacteria, fungi, and viruses. Common methodologies, such as the Kirby-Bauer Disc Diffusion Method for antibacterial assessment, agar tube dilution technique for antifungal evaluation, and in vitro experimentation using Vero and HeLa cells for antiviral studies, underscored a consistent approach to exploring these effects. The clinical application of *E. hirta* emerged prominently in the antiviral domain, specifically in managing dengue-related complications through observed platelet augmentation, hinting at a practical application. However, distinctions arose in the pathogenic focus, with antibacterial and antifungal domains concentrating on different types of bacteria and fungi, respectively. The antiviral domain uniquely incorporated information about traditional use and community awareness, a dimension absent in the other two.

Furthermore, age-related differences were introduced in the antiviral domain, indicating a potential variability in *E. hirta*'s efficacy based on patient age, a consideration not explicitly addressed in the antibacterial and antifungal sections. Overall, while these three collectively revealed the diverse antimicrobial potential of *E. hirta*, the nuanced differences highlighted the multifaceted nature of its applications in addressing a range of health challenges.

Conclusion

The results encompassing phytochemical analysis, antimicrobial mechanisms, antibacterial, antifungal, and antiviral activities of *E. hirta* revealed its multifaceted medicinal potential. Phytochemical studies identified polyphenols, flavonoids, tannins, gallic acid, quercetin, and other compounds, contributing to diverse therapeutic properties. The antibacterial properties were evident against a spectrum of gram-negative and gram-positive bacteria, showcasing effectiveness in conditions like UTIs and pneumonia. The inhibitory effects highlighted the importance of extraction methods and solvent selection.

In the antifungal domain, *E. hirta* exhibited substantial activities against Dermatophytes and *Candida*, supported by varied methodologies. Antiviral properties demonstrated inhibition of SARS-CoV-2 and retroviruses, emphasizing *E. hirta*'s potential in addressing viral infections. Studies on dengue patients displayed its traditional use and clinical significance, particularly in platelet augmentation. Overall, the findings demonstrated *E. hirta* as a valuable natural resource with extensive antimicrobial effects, advocating further exploration for therapeutic applications across diverse health challenges.

Conclusively, the researchers highlighted the following key points: Firstly, *E. hirta*'s wide-ranging antimicrobial effects were emphasized by shared properties in antibacterial, antifungal, and antiviral domains. However, distinctions in pathogenic focuses, temporal variations in antifungal efficacy, observed toxicity in specific contexts, and diverse assay techniques collectively exhibited the nuanced nature of its antimicrobial potential, paving the way for further exploration as a promising natural remedy against a diverse spectrum of infectious agents. Secondly, in reference to the *E. hirta*'s inhibitory effects, a significant convergence was noted in the concentration-dependent relationship governing its potency against bacteria, fungi, and viruses, emphasizing a dose-dependent dynamic. Nonetheless, nuanced disparities also surfaced in the selection of test organisms, methodologies, solvent intricacies, and microbial sensitivity, collectively illuminating the multifaceted nature of *E. hirta*'s impact and suggesting diverse mechanisms at play against this spectrum of microorganisms. Thirdly, in relation to its medical significance, *E. hirta* demonstrated significant antimicrobial efficacy against bacteria, fungi, and viruses, highlighting its wide-ranging and consistent methodological approaches. It also unveiled unique applications, such as managing dengue-related complications, traditional use, community awareness, and age-related considerations, emphasizing the diverse nature of its potential applications in addressing various microbial infections and other emerging health challenges.

Recommendations

For future prospects, further studies can investigate other clinically significant species and strains not covered by the research included in this review in order to examine the potency of *E. hirta* against other microorganisms. Moreover, additional studies may be conducted over time to determine the varying effectiveness and resistance of various microorganisms against *E. hirta*'s antimicrobial action. Future researchers can also look into the other medicinal purposes of *E. hirta* such as its antiparasitic properties in order to expand the utility of this plant in treating various diseases and other types of infections.

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