WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 22, 138-160. Review Article ISSN 2277–7105

EXPLORING HERBAL ANTIFUNGALS: A COMPREHENSIVE REVIEW OF BIOACTIVE PHYTOCHEMICALS AND THEIR SYNERGISTIC EFFICACY

Ms. Christina Viju[1]*, Ms. Prachi Goje[2], Ms. Sayali Raut[3], Mr. Aryan Dalvi[4], Mr. Saurabh Wagh[5], Dr. Shrutika Patil[6]

*[1]TMV's Lokmanya Tilak Institute of Pharmacy, Kharghar, 410210.

Article Received on 18 October 2025,
Article Revised on 08 Nov. 2025,
Article Published on 16 Nov. 2025,

https://doi.org/10.5281/zenodo.17615134

***Corresponding Author**

Ms. Christina Viju

TMV's Lokmanya Tilak Institute of Pharmacy, Kharghar, 410210.

How to cite this Article: Ms. Christina Viju1*, Ms. Prachi Goje2, Ms. Sayali Raut3, Mr. Aryan Dalvi4, Mr. Saurabh Wagh5, Dr. Shrutika Patil6 (2025) EXPLORING HERBAL ANTIFUNGALS: A COMPREHENSIVE REVIEW OF BIOACTIVE PHYTOCHEMICALS AND THEIR SYNERGISTIC EFFICACY. "World Journal of Pharmaceutical Research, 14(22), 138–160.

ABSTRACT

Fungal infections have emerged as a significant global health issue, impacting the skin, mucous membranes, and internal organs, with increasing resistance to traditional antifungal treatments like azoles and polyenes. This situation has prompted a move towards herbal-based therapies derived from bioactive compounds such as alkaloids, flavonoids, terpenoids, and phenolics. The study examines various medicinal plants, including Nigella sativa, Rhinacanthus nasutus, Piper betel, and Pogostemon parviflorus, which demonstrate strong antifungal effects against pathogenic species like *Candida albicans* and *Trichophyton rubrum*. Their mechanisms of action involve disrupting fungal cell walls and membranes, inhibiting ergosterol biosynthesis, and interfering with mitochondrial and enzymatic functions. Furthermore, it highlights innovative formulations like antifungal gels, creams, and roll-ons that improve the stability and effectiveness of herbal extracts. It emphasizes the potential of combining herbal constituents with conventional drugs or other natural agents as a promising approach to overcoming drug resistance while reducing side effects. The review highlights the importance of integrating phytochemical research and formulation technology to create safe antifungal treatments that meet modern pharmacological standards.

KEYWORDS: Antifungal activity, Medicinal plants, Herbal formulations, Nigella sativa, Rhinacanthus nasutus, Piper betel, Pogostemon parviflorus, Phytochemicals.

1. INTRODUCTION

Fungal infections represent a significant health concern affecting millions worldwide. These infections do when colorful fungi foray and establish themselves in different corridor of the body, including the skin, nails, respiratory system, and internal organs. Fungi thrive in warm, wettish surroundings, making certain areas of the body more susceptible to infection. Common fungal infections include athlete's bottom, ringworm, candidiasis, and aspergillosis. While some fungal infections are mild and can be fluently treated with untoward results, others can be severe and potentially life- hanging, particularly for individualities with weakened vulnerable systems. rehearsing good hygiene, avoiding prolonged exposure to damp conditions, and maintaining a strong vulnerable system are essential preventative measures against fungal infections. Treatment options range from topical antifungal creams to oral specifics, depending on the inflexibility and position of the infection.[1]

Dermatophytoses are superficial fungal infections caused by dermatophytes affecting the skin, hair and/ or nails. They're also nominated as tinea infections. Dermatophytes are filamentous fungi that foray and feed on keratinized towel like skin, hair and nails, causing an infection. Dermatophytes are divided into nine rubrics, of which Trichophyton (generally affecting skin, hair and nails), Epidermophyton (generally affecting skin) and Microsporum (generally affecting skin and hair) beget infection in humans. Trichophyton rubrum is the most common insulate observed in infections of the bases, body and nails.[2]

Little is known about the molecular mechanisms that uphold the capability of these organisms to establish and maintain infection. The recent vacuity of genome sequence information and bettered inheritable manipulation have enabled experimenters to begin to identify and study the part of acridity factors of dermatophytes.[3]

1.1. EPIDEMIOLOGY

Table 1: Epidemiology of fungal infections.[4]

Fungal Organism	Pertinent Epidemiologic Characteristics
Dermatophytes	Usually single cases, men more than women, chronic, relapsing infections; rarely outbreaks occur with spread among patients and health-care workers; potential for outbreaks from pets brought into the facility
Candida	Infection almost always from patient's own endogenous flora; *Candida glabrata* more common in urinary tract and in older persons; infection more likely in those with indwelling intravenous and urinary catheters
Cryptococcus	Acquired from outside environment; may present years later as **chronic meningitis** or **dementia** in long-term care resident
Aspergillus	Acquired from outside environment; rare in long-term care facility
Zygomycoses	Acquired from outside environment; rare in long-term care facility

1.2. HERBAL PLANTS OVER SYNTHETIC DRUGS

About 8 of sanitarium admissions in the United States of America are due to adverse or lateral goods of synthetic medicines thus, people every time turn to herbal drug because they believe factory remedies are free from undesirable side goods.[5] Deaths or hospitalizations due to sauces are so rare that they're hard to find.[6] The herbal drugs contain a lot of different composites which some of them have great complications. shops substances similar as polysaccharides, bonds and tannins may modulate and modify the goods of " active factors".[7] Of course, informed knowledge of the goods of medicinal plants as well as doing a clinical trial to understand the applicable medical operation is necessary.[8]

1.3. MECHANISM OF ACTION

1.3.1. Mechanism of Action of Antifungal Essential oils and Their Individual Compounds

EOs are complex fusions of multitudinous antimicrobial composites and motes. colorful studies have anatomized the natural parcels of the main factors, similar as terpineol, eugenol, thymol, carvacrol, carvone, geraniol, linalool, citronellol, nerol, safrole, eucalyptol, limonene, and cinnamaldehyde, which substantially reflect the biophysical and natural state of the oil painting, and it's possible that the exertion of these factors is modulated by other minor factors,[9] so their exertion depends on their chemical composition and the number of main factors. thus, its medium of action, like polyphenols, can be veritably varied (Fig. 1).

1.3.1.1. Cell Wall and Cell Membrane Damage

EOs and their factors have a variety of targets, particularly the membrane and cytoplasm, and in certain situations, they fully alter the morphology of cells.[10] Fungal cell wall composition varies among species, but it generally has three polymeric factors glucan, chitin, and mannoproteins. Glucan is a polysaccharide constituted by glucose monomers linked by (1,3)-b or (1,6)- b bonds, and it's an essential element of the cell wall, and cell membrane is verified to contain ergosterol. Other factors of the fungal cell are sphingolipids, which represent a small proportion of the fungal cytoplasmic membrane and are essential for cell functions, so their inhibition results in cell death.[11]

1.3.1.2. Mitochondria Damage

The function of mitochondria is to induce energy in the fungal cell, however, in addition, they perform acridity functions, ergosterol biosynthesis, and cell wall conservation.[12] EOs can also disrupt cell membrane hyperpolarization (also known as mitochondrial membrane eventuality (MMP) mitochondrial damage) by impacting ion budgets, similar as calcium ions, flyspeck pumps, and ATP budgets, thereby reducing membrane permeability.

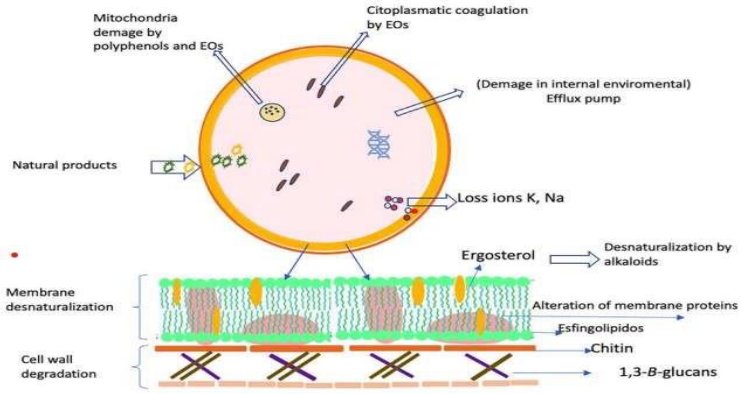

Fig 1: Different mechanism of action of natural products (essential oils, extracts, or isolate constituents). All these effects in the fungus cell can cause fungal lysis.

1.3.2. Mechanism of Action of Secondary Metabolites (Polyphenols and Alkaloids)

Plants are a great source of active substances, numerous of which are used as a defense medium against pathogens, similar as fungi. Among its active factors (secondary metabolites) are the polyphenolics and alkaloids that are the main factors of these NPs with antifungal exertion. The sesquiterpenes and monoterpenes called unpredictable NPs (EOs) are other ingredients with excellent antifungal eventuality.[13]

1.3.2.1. Inhibition of Efflux Pumps

One of the important targets in fungi is the expatriation pump of species, which is an important strategy to inhibit fungi that may be resistant, similar as C. auris, considered a major nosocomial pathogen, surfaced encyclopedically as a multidrug resistant fungus,[14] and the development of substances may affect in a remedy that replaces azole medicines.[15]

2) NIGELLA SATIVA

Nigella sativa (N. sativa, Ranunculaceae family), generally known as " black seed " or " black cumin, " is a flowering factory that grows in countries skirting the Mediterranean Sea, and in Pakistan, India, and Iran. 1. The people of the Middle East and Southeast Asian countries have used N. sativa seeds to treat diseases, similar as bronchitis, asthma, and seditious, contagious, and gastrointestinal conditions, and applied its oil painting to treat skin conditions similar as boils and eczema. N. sativa seeds play an important part in the traditional treatment of colorful conditions, especially fever, habitual headache, migraine, hypertension, and palsy. also, the excerpts of N. sativa are traditionally used as a laxative, intestinal antiprotozoal agent, and carminative.[16]

2.1. MORPHOLOGICAL CHARACTERISTICS[17]

Characteristic	Description
Family	Ranunculaceae
Stem	Slight hairy
Leaves	Shiny green, triplex
Flowers	Milky white with a slight blue or green shade at the tip
Seeds	Black, slightly twisted, three edged

2.2. SCIENTIFIC CLASSIFICATION[18]

Domain: Eukarya
Kingdom: Plantae (Plants)
Subkingdom: Tracheobionta (Vascular plants)
Super division: Spermatophyta (Seed plants)
Phylum: Magnoliophyta (Flowering plants)
Class: Magnoliopsida (Dicotyledons)
Subclass: Magnoliidae
Order: Ranunculales
Family: Ranunculaceae (Buttercup family)
Genus: Nigella

Fig. 2: Nigella Sativa (Whole plant, Flower and seeds).

2.3. ANTIFUNGAL ACTIVITY OF NIGELLA SATIVA

In both laboratory and living organism tests, N. sativa extract was used as a treatment. In a laboratory study, N. sativa seeds were found to slow the growth of various fungi, including Aspergillus fumigatus, Aspergillus flavus, Cryptococcus laurentii, Candida parapsilosis, Cryptococcus albidus, Candida albicans, Candida tropicalis, and Issatchenki aorientalis. In 2014, Mahmoudv et al. (2014) reported that N. sativa extract and its essential oil effectively reduced the growth of pathogenic fungi such as Trichophyton mentagrophytes, Microsporum gypseum, and Microsporum canis. In a living organism study, mice infected with Candida albicans were treated with an extract of black seeds, and the results showed that the treatment helped reduce the fungal infection .N. sativa seeds also inhibited the growth of Fusarium solani fungi.[19]

2.4. PHYTOCONSTITUENTS OF NIGELLA SATIVA[20]

Plant Part	Compound Category	Compound Name
Seeds	Major Bioactive Compounds	Thymoquinone, Thymohydroquinone, Dithymoquinone, p-Cymene, Carvacrol, 4-Terpineol, t-Anethol, Sesquiterpene longifolene, α- Pinene, Thymol
	Alkaloids	Nigellicimine, Nigellicimine-N-oxide, Nigellidine, Nigellicine
	Terpenes & Saponins	Alpha-hederin
	Trace Compounds	Carvone, Limonene, Citronellol
	Fatty Acids	Linoleic acid, Oleic acid, Eicodadienoic acid, Dihomolinoleic acid, Palmitic acid, Stearic acid

2.5. EXTRACTION METHODS

2.5.1. Oil extraction

2.5.1.1. Cold pressing. Black cumin seeds were pressed at room temperature (25◦C) without any thermal treatment. Mesilla was stored for one night at room temperature to separate oil

painting phase from Mesilla also oil painting was filtered over anhydrous sodium thiosulphate and cotton sludge using glass channel.

2.5.2. Microwave oven- supported birth (MAE). MAE birth was carried out with a concentrated open- vessel microwave oven system with 500 mL short- necked beaker (corner, Italy). The maximum affair power of the microwave oven outfit was 1000W with 2450 MHz of microwave oven radiation frequence. The reactor time, temperature and power were controlled using the "readily- WAVE" software package. Temperature was covered by a shielded thermocouple (ATC300) fitted directly into the sample vessel and by an external infrared detector, and controlled by a feedback to the microwave oven power regulator. The birth was continued at 45°C and atmospheric pressure until no further oil painting was attained. Temperature program was as follows 20°C to 45°C in 10 min and hold at 45°C for 40 min. A cooling system outside the microwave oven depression condensed the birth continuously. For the different birth ways, recovered BCO was stored at −18°C in darkness using amber glass bottles without headspace until analysis.[21]

3) RHINACANTHUS NASUTUS

R. nasutus is generally called as Nagamalli (Tamil). R. nasutus. Kurz (Family Acanthaceae) is a precious factory that is extensively distributed and cultivated in South China, Taiwan, India and Thailand. R. nasutus is well known as a source of flavonoids, steroids, terpenoids, anthraquinones, lignans and especially naphthoquinone analogues. colorful corridor of this factory have also been used for the treatment in conditions similar as eczema, pulmonary tuberculosis, herpes, hepatitis, diabetes, hypertension and several skin conditions nasutus is an important medicinal factory, which possesses anticancer, antifungal and antiviral parcels .It's a shrub, about 2 to 3 bases altitudinous. (Some of the bioactive factors of the factory are known to be naphthoquinones similar as rhinacanthins (A-D, G- Q), rhinacanthone and lignan groups (Yahuafai et al., 2006). It's considerably used in traditional drug, to treat liver diseases, skin conditions, peptic ulcers, helminthiasis, scurvy, inflam mation and rotundity. The methanolic root excerpt of R. nasutus was studied for its hepatoprotective effect. R. nasutus helped to save an nearly normal structure of the liver, following CCl4 – convinced liver damage, indicating its hepatoprotective goods. R. nasutus possesses a significant hepatoprotective exertion.[23]

Table 2: MORPHOLOGICAL CHARACTERISTICS.[22]

Feature	Description
Habit & Stem	Slender, erect, branched, sparsely to kindly hairy, imperishable shrub or sub-shrub. Generally 0.6 to 2 meters (occasionally over to 3 meters) in height. Stem is tender or sparsely branched with a woody base.
Leaves	Oblong, elliptic, or ovate-elliptic shape. Generally 4–10 cm in length. Narrowed and pointed at both ends (acute). Arranged opposite on the stem. May be softly pubescent (hairy).
Inflorescence	Spreading, leafy, hairy **panicle** (a branched inflorescence). Flowers generally borne in clusters.
Calyx	Green, hairy, and about 5 mm long.

3.1. EXTRACTION METHOD OF RHINACANTHUS NASUTUS

1) Leaves of Rhinacanthus nasutus (L.) were dried in a hot air oven and milled to fine powder using a mechanical grinder. The powdered plant material was macerated and shaken in 75:25 ethanol: water mixture at 60 0 C for 48 h using a bath shaker. The extract was then filtered with filter paper (Whatman Int. Ltd)and concentrated to dryness under vacuum and reduced pressure using rotary evaporator at 40°C. The concentrate was then layered on aluminium foil and freeze dried.The yield was 26.9% in terms of dry leaves weight.[22]

2) Fresh leaves of R. nasutus were collected and 1g of them was homogenized thoroughly in 10 ml of appropriate solvent. The organic extracts were dried at 60°C protected from light. The residue was weighed and dissolved in dimethyl sulfoxide (DMSO) to obtain a final concentration of 20 mg in 5 ml of DMSO. Aqueous extracts were prepared fresh when experiments were performed.[23]

3.2. SCIENTIFIC CLASSIFICATION

Kingdom: Plantae – Plants
Division: Magnoliophyta - Flowering plants
Class: Magnoliopsida
Family: Acanthaceae
Subfamily: Acanthoideae
Genus: Rhinacanthus
Species: nasutus - (L.)

Fig. 4:- Rhinacanthus Nasutus,(whole plant, flowers and leaves).

Table 3: SYNONYMS.

Synonyms	Common names
Rhinacanthus Nasutus(L.)Kurz	Snake Jasmine
Rhinacanthus Communis nees	Palakjuhi
	Nagamulla

3.3. PHARMACOLOGICAL ACTIVITIES OF RHINACANTHUS NASUTUS

3.3.1. Antifungal testing of the plant

To evaluate the antifungal activity of R. nasutus extract, tested it against three fungal species: S. cerevisiae, C. neoformans, and C. auris. The latter two are pathogenic fungi capable of causing infections. In humans, the assay began by preparing a series of dilutions of the R. nasutus extract in YPD medium, using 25% glycerol in ethanol as the solvent. A two-fold serial dilution was performed to create varying extract Concentrations, while YPD medium alone was used as the control. The fungal cultures were then dot-spotted Onto the YPD plates containing the diluted extracts. The plates were incubated at 30°C for 3 days, with Observations recorded daily to assess the growth and antifungal effects of the extracts.[24]

3.4. PHYTOCHEMICALS OF RHINACANTHUS NASUTUS[22]

Table 4: Phytochemical constituents of Rhinacanthus nasutus (L.) Kurz.

Phytochemical Class	Compound(s)	Plant Part(s)
Naphthoquinones	Rhinacanthins A–Q (A, B, C, D, G, H, I, J, K, L, M, N, O, P, Q); Rhinacanthone; Dehydro α-lapachone	Leaves, Roots, Stems
Lignans	Rhinacanthin-E, Rhinacanthin-F	Aerial parts
Flavonoids	Wogonin, Oroxylin-A, Rutin	Roots, Flowers
Sterols	Stigmasterol, β-Sitosterol	Roots, Stems
Triterpenoids	β-Amyrin, Glutinol, Lupeol	Roots

4) PIPER BETEL

Piper betel, commonly known as betel, is a significant medicinal plant belonging to the Piperaceae family, predominantly found in Southeast Asia and Eastern Malaysia. The leaves of the betel plant are highly nutritious, containing small amounts of vitamins and minerals. They are known for their antimicrobial and wound-healing properties, making them a traditional remedy for various ailments. Betel leaves have been used to treat nervous pains, coughs, and sore throats. They are rich in antioxidants like hydroxychavicol, ascorbic acid, and β-carotene. Additionally, the leaves contain enzymes and amino acids such as diastase, catalase, histidine, arginine, and lysine. Consequently, betel leaves exhibit numerous beneficial bioactivities, and their extracts are utilized in various commercial products. The methanol, ethanol, and chloroform extracts of P. betel have shown potential inhibitory effects against pathogenic bacteria, including Plasmodium berghei and Vibrio cholerae.[25]

4.1. MORPHOLOGICAL CHARACTERISTICS[25]

Category	Characteristic/Observation	Specific Detail/Timing
Assessment Focus	Morphological Traits	Utilized for identifying and evaluating betel vine varieties
Plant Parts Observed	Observed Whole Plant	Overall growth and form.
	Lateral Branches	The timing of lateral branch development was recorded from the planting date.
	Leaves	Observations focused on the fourth leaf from the tip of the lateral branch.

4.2. EXTRACT OF LEAVES OF PIPER BETEL

The Piper betel leaves were sourced from the greenhouse theater in Sivakasi, Tamil Nadu, India. The collected betel leaves were thoroughly cleaned and dried in a dark place at room temperature. The dried leaves were finely ground and stored for further processing. Samples of 7.2, 12, and 12 g of P. betel (in triplicate) were extracted using detergents, ethanol, methanol, and distilled H2O (100 ml) for 24 hours. The detergent and dH2O extracts were filtered through Whatman no. 1 filter paper and centrifuged at 5000 rpm for 10 minutes. The supernatant was carefully collected and analyzed for antimicrobial activity. Finally, the effective detergent was tested against C. albicans, and the antimicrobial activity was assessed using gas chromatography–mass spectrometry (GC-MS).[6][26]

Fig. 5: PIPER BETEL LEAVES.

4.4. PHARMACOLOGICAL ACTIVITY

4.4.1. ANTIFUNGAL ACTIVITY

Antifungal/Hydroxychavicol Hydroxychavicol, derived from the chloroform extraction of P. betel's aqueous extract, was tested for its antifungal properties against 124 fungal strains. This compound demonstrated inhibitory effects on clinically significant fungal species. It also showed a prolonged post-antifungal effect on Candida species and inhibited the emergence of mutants. These findings indicate its potential as a topical antifungal agent and as a gargle for oral Candida infections.18 Antimicrobial/Antioxidative/Anti-Haemolytic Activities Research on leaf extract revealed antibacterial, antioxidative, and anti-haemolytic properties. The antibacterial activity was attributed to sterol, which was found in significant amounts. The antioxidative and anti-hemolytic effects were linked to the high concentration and combined action of flavonoids and polyphenols 19.[27]

4.4.2. ANTIBACTERIAL ACTIVITY

In the quest for key active ingredients from natural sources that can prevent halitosis or serve as "breath fresheners," a methanol extract from fresh Piper betel leaves was evaluated using in vitro tests, including plate and broth MIC assays, biofilm assay, saliva chip model, and a conductometric method. The results suggest that allylpyrocatechol may be the active component responsible for antimicrobial activity against various obligate oral anaerobes. Table 5. Phytoconstituents of Piper betel plant Chemical Constituent Description Volatile oils Includes betel phenol, chavicol (isomeric with eugenol) Polyphenols Bioactive molecules with antioxidant properties Alkaloids Nitrogen-containing compounds with diverse bioactivities Steroids Organic compounds that may have anti-inflammatory effects Saponins Compounds known for their surfactant and medicinal properties Tannins Polyphenolic compounds with astringent properties.[28]

Table 5: Phytoconstituents of Piper betel plant.[28]

Chemical Constituent	Description
Volatile Oils	Includes betel phenol chavicol (isomeric with eugenol)
polyphenols	Bioactive molecules with antioxidant properties
Alkaloids	Nitrogen-containing compounds with diverse bioactivities
Sreroids	Organic compounds that may have anti-inflammatory effects
saponins	Compounds known for their surfactant and medical properties
Tanins	Polyphenolic compounds with astringents properties

4.3. Scientific Classification of Piper betel.[29]

Kingdom: plantae
Clade: Tracheophytes
Clade: Angiosperms
Clade: Magoliids
Order: Piperales
Family: Pipera ceae
Genus: Piper
Species: Piper betel L

5) POGOSTEMON PARVIFLORUS

Pogostemon Parviflorus Benth (P. parviflorus) belongs to Lamiaceae family, generally known as “Small – Flowered Shrub Mint” and it has a strong odor. P. parviflorus is an sweet medicinal condiment a large and different family of unfolding shops. The rubric Pogostemon includes roughly 80 species distributed generally in tropical and tropical regions of Asia, particularly in India, Sri Lanka, Myanmar, and corridor of Southeast Asia. In developing countries, the people with low income, similar as growers, people of small insulated townlets and native communities use folk drug for the treatment of common infections (Veeramuthu et al., 2006). thus, Pogostemon parviflorus splint, used in folk drug, was chosen to determine theiranti-Candida exertion. It grows in areas with high periodic downfall. Small – unfolded shrub mint is especially set up in NE India, Gujarat, Maharashtra, Rajasthan, Uttarakhand, West Bengal and SE Asia (flowers of india). This factory has antiseptic exertion and it's useful in the treatment of enteritis, eczema and mycotic enteritis (Sadeghi and Deokule, 2010). The splint of Pogostemon parviflorus contained saponins, reducing sugars, tannins, phenols and proteins, but it did n't have any glycosides, anthraquinones, alkaloids or flavonoids.[30]

5.1. MORPHOLOGICAL CHARACTERISTICS OF POGOSTEMON PARVIFLORUS[31]

Features	Description
Stem	Erect, 4-angular, slightly swollen at nodes, villous above.
Leaves	Opposite, elliptic-lanceolate, shallowly toothed, short petiole (up to 11.5 cm).
Inflorescence	Terminal/axillary spikes 2.5–8 cm long, 12 mm wide, villous peduncle.
Calyx	4–5 mm long.
Corolla	6–7 mm long
Distinctive Features	Larger spikes, villous stem, short-petioled toothed leaves.

5.2. EXTRACTION METHOD OF POGOSTEMON PARVIFLORUS

The leaves of Pogostemon parviflorus were extracted in ethanol. To 10 g of each powdered material was added 100 mL ethanol 80% (drug/solvent ratio of 1:10 w/v) in a conical flask for maceration. Flask was then plugged with cotton and placed on a rotary shaker at 190-220 rpm for 72 h at room temperature.[7] Finally, the suspension was filtrated through a Buckner funnel and Whatman filter paper #1. The ethanolic extract was evaporated to dryness in an oven or in a water bath at 45°C. One gram of the dried extract was then dissolved in 1 mL 100 % dimethyl sulfoxide (DMSO). The final concentration of each extract was adjusted to 1000 mg/mL. Dermatophyte isolates.[32]

5.3. SCIENTIFIC CLASSIFICATION

Kingdom: Plantae
Division (Phylum): Magnoliophyta
Order: Lamiales
Family: Lamiaceae (Mint family)
Genus: Pogostemon
Species: *Pogostemon parviflorus* Benth.

Fig. 6: Pogostemon parviflorus (Leaves, flowers)

5.4. Pharmacological Activities of *Pogostemon parviflorus*

5.4.1. Antifungal and Antidermatophytic Activity

In this study, in vitro antifungal exertion of Pogostemon parviflorus splint excerpts were estimated against three different rubrics of dermatophytes including Microsporum, Trichophyton and Epidermophyton, using the agar dilution system. The ethanolic excerpt of Pogostemon parviflorus splint inhibited the growth of tested dermatophytes at different attention. The ethanolic excerpt of Pogostemon parviflorus splint fully averted the growth of tested dermatophytic species, with minimal inhibitory attention (MIC) values between 2.5- 10 mg/ mL. The minimal fungicidal attention (MFC) values of this factory were also in the range of 2.5- 10 mg/ mL. Results of phytochemical webbing tests indicated that the splint of Pogostemon parviflorus contained saponins, reducing sugars, tannins, phenols and proteins, but it did n't have any glycosides, anthraquinones, alkaloids or flavonoids. Results of High Performance Thin Subcaste Chromatography (HPTLC) studies indicated that the ethyl acetate excerpt of Pogostemon parviflorus leaves included triterpenes, as 10 and 14 peaks of ultra violet (UV) immersion were observed in 254 nm and 366 nm, independently. Hence, triterpenes may be responsible for antidermatophytic exertion of this factory.[3] The ethanolic and methanolic splint excerpts displayed significant inhibitory goods against several Candida species like C. albicans, C. glabrata, C. tropicalis, C. dubliniensis[1] A study by Sonam et al. (2019) further verified the antifungal exertion of DMSO splint excerpts of P. parviflorus against Candida albicans, pressing its eventuality for managing oral fungal infections, particularly in vulnerable compromised and cancer cases.[31]

5.4.2. Anti-inflammatory and Cytoprotective Effects

The triterpenes and sesquiterpenoid lactones (like parvinolide and epoxyparvinolide) identified in P. parviflorus have shown anti-inflammatory potential. These compounds are known to suppress inflammatory mediators such as COX-2, NF-κB, and TNF-α, reducing inflammation and tissue damage.[31]

Table 6: Phytochemicals of Pogostemon Parviflorus.[30-32]

Phytochemical Class	Presence	Pharmacological Significance
Saponins	Present	Exhibit strong antifungal, cytotoxic, and membrane-permeabilizing effects; enhance activity of other bioactives.
Tannins	Present	Show antimicrobial, antioxidant, and wound-healing properties; precipitate microbial proteins and inhibit fungal enzymes.
Triterpenes	Major	Responsible for antifungal, anti-inflammatory, and

	(abundant)	antioxidant activities; inhibit ergosterol biosynthesis in fungi.

5.5. SYNONYMS

Synonym	Common Name
Pogostemon Championii Prain	**Small-Flowered Shrub Mint**

6) SYNERGISTIC COMBINATION

6.1. Rhinacanthus Nasutus

6.1.1. Rhinacathus Nasutus with nicotinamide-streptozotocin combination

Rhinacanthin rich extracts (RRE) offers remarkable benefits as a cover to RC in term of lower product cost, green birth process and potentially original or advanced bioactivity due to synergism amongst RRE factors (17 – 19). In the present study, RRE was prepared by simple, terrain-friendly, green birth processes to probe itsanti-hyperglycemic and anti-hyperlipidemic goods in nicotinamide- streptozotocin convinced diabetic rats. In silico studies were also conducted to prognosticate pharmacokinetic and toxin profile of Rhinacanthin. By this method, Diabetes was confirmed from the higher level of fasting blood glucose (FBG) using a glucometer (One Touch, LifeScan, Zug, Switzerland) after 72 h of STZ injection. Theanimal's tail vein was pricked to collect blood for the FBG determination. Animals with an FBG above 300 mg/dL having symptoms such as hyperphagia, polydipsia and polyuria were marked as diabetic.[33]

6.1.2 Rhinacanthus Nasutus in synergy with Rhinacanthins

The cytochrome P450 monooxygenases play a major part in germicide detoxification and come a target for development of germicide synergists. In this study, a collection of rhinacanthins(rhinacanthin- D,- E,- G,- N,- Q, and- H in purified form, in to purified rhinacanthin- B and- C, were insulated. These composites displayed colorful degrees of inhibition against benzyloxyresorufin- O- debenzylation intermediated by CYP6AA3 and CYP6P7 which were intertwined in pyrethroid resistance in vector of Anopheles malaria vector. Inhibitory modes and kinetics were determined for each of rhinacanthins.[34]

B) Piper Betel

1) Piper betel L. (betel quid) shows synergistic antimicrobial action when combined with conventional antibiotic

Piper betel L. has shown strong synergistic antimicrobial activity when combined with conventional antibiotics. The acetone (ACE) and ethyl acetate (EAE) extracts exhibited the

highest synergy. The EAE–Streptomycin and ACE–Streptomycin combinations (50:50 and 70:30) were effective against E. coli, P. acnes, and S. epidermidis. Similarly, the ACE–Chloramphenicol (70:30) combination showed the greatest synergistic effect (ΣFIC = 0.09) against Pseudomonas aeruginosa, along with synergy against S. aureus, S. pyogenes, and P. acnes. These findings suggest that P. betel can potentiate antibiotic action and may serve as a natural adjuvant in managing multidrug-resistant bacterial infections.[35]

C) Nigella Sativa

1) Synergistic Combination: Honey and *Nigella sativa*

A synergistic interaction between honey and *Nigella sativa* seed oil was demonstrated in an excisional wound model in rats. The mixture (1:1) significantly reduced wound surface area across all healing stages compared to individual applications of honey or *N. sativa* oil. This enhanced activity is attributed to the multifactorial pharmacological mechanisms of both components—honey contributes flavonoids, phenolic acids, and amino acids that stimulate collagen synthesis and fibroblast proliferation, while *N. sativa* provides thymoquinone with potent antioxidant, antibacterial, and anti-inflammatory properties. Their combined use not only accelerated tissue repair but also minimized potential side effects of single-agent therapy. Thus, this combination exhibits **a** potent synergistic wound healing effect and can serve as a promising natural therapeutic formulation for cutaneous injuries.[36]

2) Synergistic Combination: *Moringa oleifera*, *Cinnamomum verum*, and *Nigella sativa*

The synergistic combination of *Moringa oleifera*, *Cinnamomum verum* (cinnamon), and *Nigella sativa* (black seed) essential oils has demonstrated potent antimicrobial efficacy against multidrug-resistant *Staphylococcus aureus*. According to Abu-Hussien et al. (2025), the blend of these three oils in an optimal ratio of 1:1:1 (0.338:0.307:0.355 mL v/v) exhibited a strong synergistic effect with a fractional inhibitory concentration index (∑FIC) of 0.27, confirming enhanced antibacterial potency. The combined formulation significantly reduced the minimum inhibitory concentration (MIC) values of the individual oils from 3.12, 0.78, and 6.25 µg/mL to 0.25, 0.06, and 0.78 µg/mL, respectively, surpassing the effectiveness of standard antibiotics such as tetracycline. Among the tested pairings, the *Moringa–Cinnamon* and *Cinnamon–Nigella sativa* interactions displayed the most pronounced synergistic responses, attributed to the complementary actions of their phytochemicals. Gas chromatography–mass spectrometry (GC/MS) analysis revealed the presence of bioactive constituents such as cinnamaldehyde, linoleic acid, and palmitic acid methyl esters, which

contributed to the observed antimicrobial[1] synergy by enhancing membrane disruption and oxidative stress in bacterial cells. Furthermore, cytotoxicity studies confirmed the biocompatibility of the optimized oil mixture, showing 97.6% viability in human skin fibroblast cells after 24 hours of exposure. Collectively, this rationally designed phytochemical formulation demonstrates a remarkable synergistic antibacterial effect, providing a safe and effective natural alternative to combat antibiotic-resistant *Staphylococcus aureus* infections.[37]

D) Pogostemon Parviflorus

1) Synergistic Combination: *Pogostemon parviflorus* Extracts and Antifungal Agents

The study by Najafi and Sadeghi-Nejad (2011) highlighted the potent anti-Candida synergistic activity of *Pogostemon parviflorus* leaf extracts against various pathogenic *Candida* species, including *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. dubliensis*. Both ethanol and methanol extracts of *P. parviflorus* demonstrated significant antifungal efficacy when compared with standard antifungal drugs such as ketoconazole. The ethanol extract showed a stronger inhibitory effect, with mean minimum inhibitory concentrations (MICs) of 5.7 mg/mL, while the methanol extract exhibited an MIC of 6.6 mg/mL. The inhibition zones ranged from 8–20 mm, comparable to the standard antifungal agent. Notably, when *P. parviflorus* extracts were evaluated in combination with other antifungal compounds, a synergistic effect was observed, enhancing antifungal potency and reducing the required effective concentrations. This synergism is attributed to the presence of bioactive phytoconstituents such as flavonoids, phenols, tannins, and terpenoids that disrupt fungal cell membrane integrity and inhibit ergosterol synthesis, a vital component of fungal cell walls. The combined antifungal action not only inhibited fungal proliferation but also prevented resistance development. The results suggest that ethanol extract of *P. parviflorus* possesses superior synergistic anti-Candida activity and could be utilized in combination with conventional antifungal agents to formulate natural, broad-spectrum antifungal therapies.[38]

7) ADVANCED HERBAL FORMULATION

7.1. Nigella Sativa hydrogel

Preparation of quince seeds gum hydro- gel. The quince seeds were bought from the original herbal drug request of Shahroud, Iran. They were washed and disinfected using ultraviolet germicidal irradiation (Honeywell RUVLAMP1, USA). The seeds were dried in the roaster at 50 °C for 8 hours prior to grinding and filtering through sieve (1.18 mm). The persecuted

seeds (10 g) were mixed with distilled water (200 mL) and warmed in a water bath at 80°C for 40 twinkles to form gum hydrogel (5 w/ v). The hy- drogel was rained from 11 v/ v rate of ethanol water result and collected. Unused hydrogel was stored at 4°C. Essential oil painting birth. The essential canvases from the seeds of Nigella sativa, the peels of Cinammon verum and Citrus sinensis were uprooted using a Clevenger outfit. Compactly, 50g dried greasepaint of each factory accoutrements was placed in a 500 ml Cleveng- er outfit containing 300 ml of distilled water and brought to the boiling point. The birth process was completed in 2.5 hours. Equal volume admixture of each essential oil painting was used for antifungal experiments.[39]

7.2. Topical anti-fungal sticks of rhinacanthus nasutus

Topical antifungal sticks containing the methanolic excerpts of Rhinacanthus nasutus were successfully designed and formulated using a varied rate of cut 400 and cut 4000 and admixture of cocoa adulation, carnauba and notions wax. Al the antifungal sticks formulated as per Table 1 displayed considerable hardness 3.00 to 4.00 kg/ cm2 and performed weight variation test with all sticks measuring approximately 10 gm. In vitro release study showed that flavonoids had advanced dissipation rate in the cut grounded antifungal stick. The diffusivity of flavonoids from the Cocoa adulation sticks was minimum which may be attributed to its high lipophilicity and affinity for the active component. The medium of release was supported with high retrogression measure of Hixson Crowell for cut sticks supporting corrosion- grounded release medium of the expression. Antifungal test showed considerable exertion against five strains of Aspergillus fumigatus, Aspergillus niger, Penicillium chrysogenum, and Penicillium italicum at a attention of 80µg/ ml. The expression PG1 displayed similar exertion preceding possible topical operation of the designed expression. The exploration work laid a strong foundation for the developed expression to be considered as topical lozenge form in dermatological fungal infections.[40]

7.3. Herbal gel formulation of Piper betel The creation of sixteen betel oil gel formulations involved using four different gelling agents (Carbopol 934, HPMC, NaCMC, and Sodium Alginate) and two permeation enhancers (DMSO and PEG). Initially, methyl and propyl paraben were dissolved in distilled water. The polymers were then prepared to form the gel bases: Carbopol 934 was soaked and neutralized with triethanolamine; HPMC and NaCMC were dispersed and soaked overnight; and Sodium Alginate was triturated and soaked. Meanwhile, accurately measured betel oil was separately dissolved into weighed amounts of

PEG and DMSO. These oil/enhancer mixtures were then incorporated into the polymer gel bases with continuous stirring, ensuring no air was trapped. Finally, glycerin and the remaining purified water were added sequentially with stirring to reach the final required weight for each formulation. After preparation, all gels underwent evaluation tests. The observation of precipitation or turbidity in some batches suggested potential incompatibility within the system, possibly due to interactions between excipients like glycerin or PEG, necessitating further stability analysis.[41]

Table 7: Antifungal Activity and Mechanisms of Selected Medicinal Plants.

Plant Species	Key Phytochemicals	Mechanism of Antifungal Action	Target Fungal Species
Nigella sativa (Black cumin)	Thymoquinone, Thymohydroquinone, Nigellone, Carvacrol, p-Cymene, α-Pinene	Disrupts fungal cell membrane integrity; inhibits ergosterol synthesis; induces oxidative stress	Candida albicans, Aspergillus niger, Aspergillus fumigatus, Trichophyton rubrum
Rhinacanthus nasutus (Snake jasmine)	Rhinacanthin-C, Rhinacanthin-D, Lupeol, β-Sitosterol, Stigmasterol	Interferes with fungal cell wall synthesis; inhibits hyphal growth; induces mitochondrial dysfunction	Candida albicans, Cryptococcus neoformans, Trichophyton mentagrophytes
Piper betel (Betel leaf)	Eugenol, Chavicol, Hydroxychavicol, Caryophyllene, Safrole	Causes membrane disruption via lipid peroxidation; inhibits spore germination; suppresses fungal enzymatic activity	Candida albicans, Aspergillus flavus, Fusarium oxysporum, Penicillium chrysogenum
Pogostemon parviflorus (Patchouli species)	Patchouli alcohol, Pogostone, α-Bulnesene, Caryophyllene, Limonene	Disrupts fungal plasma membrane; causes leakage of intracellular components; inhibits ergosterol biosynthesis	Candida albicans, Aspergillus fumigatus, Fusarium solani, Microsporum gypseum

CONCLUSION

Herbal antifungals provide a safer and more environmentally friendly alternative to synthetic drugs, helping to minimize toxicity and resistance issues. Plants such as *Nigella sativa*, *Rhinacanthus nasutus*, and *Piper betel* exhibit potent antifungal activity by disrupting cell membranes and inhibiting ergosterol synthesis. Their bioactive compounds act synergistically to enhance overall efficacy. Moreover, the development of herbal-based formulations like gels and creams can further improve stability and ease of application. In essence, plant-derived antifungals show significant potential for sustainable and effective management of fungal infections.

REFERENCES

1. de Pauw BE. What are fungal infections? Mediterr J Hematol Infect Dis., 2011; 3(1): e2011001.
2. Jartarkar SR, Patil A, Goldust Y, Cockerell CJ, Schwartz RA, Grabbe S, et al. Pathogenesis, immunology and management of dermatophytosis. J Fungi., 2021; 8(1): 39.
3. Achterman RR, White TC. Dermatophyte virulence factors: identifying and analyzing genes that may contribute to chronic or acute skin infections. Int J Microbiol., 2012; 2012(1): 358305.
4. Kauffman CA, Hedderwick SA. Fungal infections. Infect Manag Geriatr Long Term Care Facil., 2006: 479–98.
5. Philomena G. Concerns regarding the safety and toxicity of medicinal plants – An overview. J Appl Pharm Sci., 2011; 1(6): 40–4.
6. Nasri H. Cisplatin therapy and the problem of gender-related nephrotoxicity. J Nephropharmacol., 2013; 2(2): 13–4.
7. Rafieian-Kopaei M, Baradaran A, Rafieian M. Oxidative stress and the paradoxical effects of antioxidants. J Res Med Sci., 2013; 18(7): 628.
8. Rafieian-Kopaei M. Medicinal plants and the human needs. J HerbMed Pharmacol., 2012; 1(1): 1–2.
9. Bakkali F, Averbeck S, Averbeck D, Idaomar M. Biological effects of essential oils: a review. Food Chem Toxicol., 2008; 46(2): 446–75.
10. Nazzaro F, Fratianni F, De Martino L, Coppola R, De Feo V. Effect of essential oils on pathogenic bacteria. Pharmaceuticals., 2013; 6(12): 1451–74.
11. Vicente MF, Basilio A, Cabello A, Peláez F. Microbial natural products as a source of antifungals. Clin Microbiol Infect., 2003; 9(1): 15–32.
12. Dagley MJ, Gentle IE, Beilharz TH, Pettolino FA, Djordjevic JT, Lo TL, et al. Cell wall integrity is linked to mitochondria and phospholipid homeostasis in Candida albicans through the activity of the post-transcriptional regulator Ccr4-Pop2. Mol Microbiol., 2011; 79(4): 968–89.
13. Marena GD, Ramos MADS, Carvalho GC, Junior JAP, Resende FA, Correa I, et al. Natural product-based nanomedicine applied to fungal infection treatment: A review of the last 4 years. Phytother Res., 2022; 36(7): 2710–45.
14. Ademe M, Girma F. Candida auris: from multidrug resistance to pan-resistant strains. Infect Drug Resist., 2020; 13: 1287–94.

15. Holmes AR, Cardno TS, Strouse JJ, Ivnitski-Steele I, Keniya MV, Lackovic K, et al. Targeting efflux pumps to overcome antifungal drug resistance. Future Med Chem., 2016; 8(12): 1485–501.
16. Mashayekhi-Sardoo H, Rezaee R, Karimi G. Nigella sativa (black seed) safety: an overview. Asian Biomed Res Rev News., 2020; 14(4): 127.
17. Thilakarathne RCN, Madushanka GDM, Navaratne SB. Morphological characteristics of black cumin (Nigella sativa) seeds. [Journal name not provided], 2018.
18. Sharma NK, Ahirwar D, Jhade D, Gupta S. Medicinal and pharmacological potential of Nigella sativa: a review. Ethnobot Leaflets, 2009; 2009(7): 11.
19. Balyan P, Shinde S, Ali A. Potential activities of nanoparticles synthesized from Nigella sativa L. and its phytoconstituents: an overview. J Phytonanotechnol Pharm Sci., 2021; 1(2): 1–9.
20. Ahmad AA, Husain AH, Mujeeb MM, Khan SA, Najmi AK, Siddique NA, et al. A review on therapeutic potential of Nigella sativa: a miracle herb. [Journal name not provided], 2013.
21. Kiralan M, Özkan G, Bayrak A, Ramadan MF. Physicochemical properties and stability of black cumin (Nigella sativa) seed oil as affected by different extraction methods. Ind Crops Prod., 2014; 57: 52–8.
22. Sattar MA, Abdullah NA, Khan AH, Noor AM. Evaluation of antifungal and antibacterial activity of a local plant Rhinacanthus nasutus (L.). J Biol Sci., 2004; 4(4): 498–50
23. Nirmaladevi R, Padma PR, Kavitha D. Analyses of the methanolic extract of the leaves of Rhinacanthus nasutus. J Med Plants Res., 2010; 4(15): 1554–60.
24. Khongthongdam M, Jantarach T, Phetruen T, Chanarat S. Antifungal potential of Rhinacanthus nasutus extracts against pathogenic fungi including Cryptococcus neoformans and Candida auris.
25. Nayaka NMDMW, Sasadara MMV, Sanjaya DA, Yuda PESK, Dewi NLKAA, Cahyaningsih E, et al. Piper betel (L): recent review of antibacterial and antifungal properties, safety profiles, and commercial applications. Molecules., 2021; 26(8): 2321.
26. Selvaraj GK, Wilson JJ, Kanagaraj N, Subashini E, Thangavel S. Enhanced antifungal activity of Piper betel against Candida albicans and in silico analysis with its virulent protein. Biomed Biotechnol Res J., 2022; 6(1): 73–80.
27. Shah SK, Garg G, Jhade D, Patel N. Piper betel: phytochemical, pharmacological and nutritional value in health management. Int J Pharm Sci Rev Res., 2016; 38(2): 181-9.

28. Vikash C, Shalini T, Verma NK, Singh DP, Chaudhary SK, Asha R. Piper betel: phytochemistry, traditional use and pharmacological activity – a review. Int J Pharm Res Dev., 2012; 4(4): 216–23.
29. Pradhan D, et al. Golden heart of the nature: *Piper betel* L. J Pharmacogn Phytochem., 2013; 1(6).
30. Najafi S, Nejad BS. Screening of Pogostemon parviflorus Benth. for anti-Candida activity. Afr J Microbiol Res., 2011; 5(6): 657–60.
31. Yuan L, Tan G, Zhang W, Xue B, Deng J, Liu L, et al. Molecular and morphological evidence for a new species of Pogostemon (Lamiaceae) from Hainan Island, China. Phyto Keys., 2022; 188: 177.
32. Sadeghi-Nejad B, Deokule SS. Antidermatophytic activity of Pogostemon parviflorus Benth. Iran J Pharm Res., 2010; 9(3): 279.
33. Shah MA, Reanmongkol W, Radenahmad N, Khalil R, Ul-Haq Z, Panichayupakaranant P. Anti-hyperglycemic and anti-hyperlipidemic effects of rhinacanthins-rich extract from Rhinacanthus nasutus leaves in nicotinamide-streptozotocin induced diabetic rats. Biomed Pharmacother., 2019; 113: 108702.
34. Kotewong R, Pouyfung P, Duangkaew P, Prasopthum A, Rongnoparut P. Synergy between rhinacanthins from Rhinacanthus nasutus in inhibition against mosquito cytochrome P450 enzymes. Parasitol Res., 2015; 114(7): 2567–79.
35. Taukoorah U, Lall N, Mahomoodally F. Piper betel L.(betel quid) shows bacteriostatic, additive, and synergistic antimicrobial action when combined with conventional antibiotics. South African Journal of Botany. 2016 Jul 1; 105: 133-40.
36. Javadi SM, Hashemi M, Mohammadi Y, MamMohammadi A, Sharifi A, Makarchian HR. Synergistic effect of honey and Nigella sativa on wound healing in rats. Acta cirurgica brasileira., 2018 Jun; 33(06): 518-23.
37. Abu-Hussien SH, Nasry AR, Samy Z, El-Sayed SM, Bakry A, Ebeed N, Elhariry H, ElNoby T. Synergistic antimicrobial activity of essential oils mixture of Moringa oleifera, Cinnamomum verum and Nigella sativa against Staphylococcus aureus using L-optimal mixture design. AMB Express., 2025 Jan 28; 15(1): 15.
38. Sharanappa R, Vidyasagar GM. Anti-Candida activity of medicinal plants: a review. Int J Pharm Pharm Sci., 2013; 5: 9–16.
39. Mirzaii M, Yaeghoobi M, Afzali M, Amirkhalili N, Mahmoodi M, Sajirani EB. Antifungal activities of quince seed mucilage hydrogel decorated with essential oils of

Nigella sativa, *Citrus sinensis* and *Cinnamomum verum*. Iran J Microbiol., 2021; 13(3): 352.

40. Ansari MT, Sami F, Majeed S, Hasnain MS, Badgujar VB. Design and evaluation of topical herbal antifungal stick containing extracts of Rhinacanthus nasutus. J Herb Med., 2019; 17: 100290.
41. Satpathy B, Sahoo M, Sahoo P, Patra SR. Formulation and evaluation of herbal gel containing essential oils of piper betel against skin infecting pathogens. Int. J. Res. Pharm. Sci., 2011; 2(3): 373-8.