

GARLIC AND CLOVE ESSENTIAL OILS AS POTENTIAL TOPICAL ANTIFUNGAL AGENTS PHYTOCHEMISTRY, MECHANISMS, FORMULATION STRATEGIES AND NANO-ENABLED DELIVERY

Lochan Markande*¹, Dr. Anandmahalwar², Vikas Kumar Sahu³

¹Student of M Pharmacy, (Pharmaceutics).

²Professor Faculty of Health and Allied Sciences.

³Assistant Professor Faculty of Health and Allied Sciences.

Article Received on 15 Sept. 2026,
Article Revised on 05 Oct. 2026,
Article Published on 16 Oct. 2026,

<https://doi.org/10.5281/zenodo.23383775>

*Corresponding Author

Lochan Markande

Student of M Pharmacy,
(Pharmaceutics).



How to cite this Article: Lochan Markande*, Dr. Anandmahalwar, Vikas Kumar Sahu (2026). Garlic And Clove Essential Oils As Potential Topical Antifungal Agents Phytochemistry, Mechanisms, Formulation Strategies And Nano-Enabled Delivery. World Journal of Pharmaceutical Research, 15(20), 373-393.

This work is licensed under Creative Commons Attribution 4.0 International license.

ABSTRACT

Superficial fungal infections and reduced susceptibility to established antifungal drugs have encouraged investigation of plant-derived topical agents. Garlic (*Allium sativum*) and clove (*Syzygium aromaticum*) contain chemically distinct constituents with experimental antifungal activity. This narrative review examines their phytochemistry, proposed mechanisms, formulation strategies, combination potential and dermal safety. Evidence concerning purified allicin and garlic extracts is distinguished from evidence concerning distilled garlic essential oil, which is dominated by allyl polysulfides. Clove oil is typically rich in eugenol and has shown in-vitro activity against *Candida*, *Aspergillus* and dermatophytes. Proposed actions include membrane perturbation and disruption of cellular enzymes and redox processes, although their contribution depends on the preparation and test organism.

Combining the two oils is a plausible research strategy, but synergistic activity requires quantitative confirmation. Nanoemulsions, lipid carriers and hydrogels offer formulation options for improving dispersion and local delivery; their benefits must be demonstrated against suitable controls. Chemical variability, instability, dermal toxicity and limited direct evidence for standardized combinations remain barriers to translation. Future studies should integrate chemical characterization, susceptibility and interaction testing, skin-safety

assessment, formulation stability and clinical validation. Garlic–clove topical formulations remain investigational, and laboratory activity alone does not establish clinical effectiveness.

KEYWORDS: *Allium sativum*; *Syzygium aromaticum*; essential oils; topical antifungals; eugenol; nanoformulation; combination therapy.

1. INTRODUCTION

Fungal infections represent an important global health problem, ranging from superficial dermatophytosis and mucocutaneous candidiasis to severe invasive fungal diseases. Their clinical burden is particularly important among immunocompromised and otherwise vulnerable populations. Global estimates indicate a substantial burden of skin, nail and hair fungal infections, together with mucosal and invasive fungal diseases. Inadequate diagnosis, limited therapeutic options and increasing antifungal resistance further complicate disease management.^[1,2]

Superficial dermatophytosis remains one of the most common fungal infections worldwide. The recent emergence and international spread of *Trichophyton indotineae* has created an additional therapeutic challenge because many isolates show reduced susceptibility or resistance to terbinafine, one of the major agents used for dermatophyte infections.^[3]

Conventional antifungal therapy includes major drug classes such as polyenes, azoles, echinocandins and allylamines. Although these agents remain essential for clinical management, their use may be limited by toxicity, drug interactions, restricted therapeutic options, treatment failure and development of resistance. For superficial infections, prolonged or inappropriate treatment may further contribute to therapeutic failure. These limitations have stimulated interest in alternative and complementary antifungal compounds, including plant-derived bioactive molecules and essential oils.^[4,5]

Essential oils are complex mixtures of volatile and predominantly lipophilic phytochemicals. Their chemical composition depends on plant species, cultivar, geographical origin, environmental conditions, extraction procedure and storage. Because of their chemical complexity, essential oils may exert antimicrobial effects through several mechanisms rather than through a single molecular target. Reported mechanisms include alteration of microbial membranes, increased permeability, interference with enzymes and cellular metabolism, oxidative imbalance and inhibition of biofilm-associated processes.^[5]

Garlic (*Allium sativum*) and clove (*Syzygium aromaticum*) are particularly interesting because their major bioactive constituents belong to chemically different classes. Garlic is characterized by sulfur-containing compounds, especially allicin and related organosulfur compounds, whereas clove essential oil is characteristically rich in eugenol.^[6-9] Allicin is generated after disruption of garlic tissue through the interaction of alliin and alliinase and is chemically reactive toward thiol-containing cellular components. Eugenol, the principal constituent of many clove oils, has demonstrated antimicrobial activity and can interact with microbial membranes and other cellular targets.^[6-9]

Experimental studies have reported antifungal effects of garlic-derived compounds against *Candida* species and of clove oil against *Candida*, *Aspergillus* and dermatophytes.^[6,10] In particular, Pinto et al. demonstrated antifungal activity of clove essential oil and eugenol against clinical and reference strains belonging to these fungal groups.^[10]

Despite this potential, direct topical use of essential oils presents several formulation challenges. High volatility, poor aqueous solubility, oxidation, chemical instability, intense odor and possible skin irritation may limit their pharmaceutical application. Encapsulation and advanced delivery systems, including nanoemulsions, lipid nanoparticles and hydrogels, may improve dispersion, stability, controlled release and local skin delivery.^[11-15] Essential-oil stability is particularly important because oxidation and other degradation processes may alter both chemical composition and biological activity.^[11]

A combination of garlic and clove oils is conceptually attractive because their major constituents have different chemical structures and potentially complementary mechanisms. However, inhibition produced by two agents together should not automatically be described as synergy. Quantitative methods such as checkerboard microdilution, fractional inhibitory concentration index (FICI), time-kill analysis and biofilm assays are required to establish whether the interaction is synergistic, additive, indifferent or antagonistic.^[16]

Therefore, this review discusses the botanical and phytochemical characteristics of garlic and clove essential oils, their antifungal mechanisms and activity against clinically relevant fungal pathogens, formulation challenges, nano-enabled topical delivery systems, potential combination effects, safety considerations and future research directions.

Scope of the review

This narrative review considers the cited literature on phytochemistry, experimental antifungal effects, topical delivery and safety. It distinguishes findings for individual constituents from whole oils and separates established experimental observations from proposed combination and formulation strategies. The discussion is qualitative and does not provide a systematic evidence synthesis or pooled efficacy estimate.

2. Botanical Profile and Phytochemistry of Garlic and Clove

2.1 Garlic (*Allium sativum*)

Garlic (*Allium sativum* L.) is an important medicinal and culinary plant belonging to the family Amaryllidaceae. Its biological properties are largely associated with sulfur-containing compounds. Freshly damaged garlic tissue rapidly produces allicin from the amino-acid derivative alliin through the action of the enzyme alliinase. Allicin is relatively reactive and can subsequently undergo transformation to several other organosulfur compounds.^[6,7]

Garlic preparations contain different sulfur compounds depending on processing. Distilled essential oil is generally rich in diallyl disulfide, diallyl trisulfide and other allyl polysulfides, whereas allicin is associated with freshly disrupted tissue and selected extracts.^[21] Purified allicin, crude garlic extracts and distilled oil should therefore be treated as distinct test materials.

Allicin has attracted particular interest because of its broad biological activity. It reacts with sulfhydryl groups in proteins and enzymes, providing a mechanistic explanation for several antimicrobial effects. Antifungal activity has been reported particularly against *Candida albicans*.^[6]

However, allicin is chemically unstable and garlic-derived preparations can undergo substantial changes during processing and storage. This instability presents an important challenge for pharmaceutical formulation. A formulation designed to preserve or control the availability of biologically active sulfur compounds may therefore be more useful than direct application of an unstandardized garlic preparation.

2.2 Clove (*Syzygium aromaticum*)

Clove (*Syzygium aromaticum* (L.) Merr. & L.M. Perry) belongs to the family Myrtaceae. The dried flower buds are the principal commercial source of clove essential oil. Clove oil

generally contains a high proportion of eugenol together with other constituents, including eugenyl acetate and β -caryophyllene.^[8,9]

Eugenol is responsible for a substantial proportion of the biological activity attributed to clove oil. Its antimicrobial properties have been extensively reviewed and include effects against bacteria and fungi. The activity of eugenol-containing essential oils is influenced not only by eugenol concentration but also by interactions among minor constituents.^[9]

Pinto et al. characterized a clove essential oil containing approximately 85% eugenol and evaluated its activity against *Candida*, *Aspergillus* and dermatophyte species. Both the complete essential oil and eugenol showed antifungal activity, demonstrating the relevance of clove oil as a candidate for further topical investigation.^[10]

2.3 Comparative Phytochemical Features

Garlic and clove essential oils differ substantially in their dominant chemical constituents. Garlic is principally associated with organosulfur chemistry, while clove oil is generally dominated by phenylpropanoid chemistry, particularly eugenol.^[6-9] This chemical difference provides a theoretical basis for investigating their combined use.

Geographical origin, cultivation, extraction and storage can alter essential-oil composition. GC–MS profiling is appropriate for volatile constituents and batch comparison.^[11] An allicin-containing preparation additionally requires an analytical method suitable for its reactive constituents; the presence of allicin should not be inferred from the botanical name alone.^[7]

Table 1: Comparative phytochemical and antifungal characteristics of garlic and clove essential oils.

Feature	Garlic essential oil (<i>Allium sativum</i>)	Clove essential oil (<i>Syzygium aromaticum</i>)	Refs.
Major bioactive constituents	Diallyl disulfide, diallyl trisulfide and related allyl polysulfides	Eugenol, eugenyl acetate and β -caryophyllene	[8,9,21]
Predominant chemical class	Organosulfur compounds	Phenylpropanoid/phenolic compounds	[6–9]
Major active compound formation	Fresh-tissue allicin chemistry differs from the polysulfide profile of distilled oil	Eugenol occurs naturally at high concentration in clove essential oil	[7,21]
Principal proposed	Allicin shows thiol reactivity; this cannot be	Membrane interaction, increased permeability and disruption of membrane-	[6,9,10]

antifungal mechanism	assumed for whole distilled oil	associated functions	
Reported fungal targets	Candida evidence includes allicin; preparation identity affects interpretation	Candida, Aspergillus and dermatophytes	[6,10]
Major formulation challenges	Chemical instability and oxidation of sulfur-containing compounds	Volatility, oxidation and concentration-dependent dermal irritation/cytotoxicity	[7,11,17]
Potential topical delivery systems	Nanoemulsions, lipid nanoparticles and hydrogels	Nanoemulsions, lipid nanoparticles and hydrogels	[12–15]
Standardization requirement	Chemical characterization and marker-based quality control	GC–MS profiling and marker-based standardization	[8,9,11]
Current research status	Promising predominantly preclinical evidence	Promising experimental evidence with established activity against several fungal groups	[6,9,10]

3. Phytochemical Basis and Mechanisms of Antifungal Activity

3.1 Garlic Organosulfur Compounds

The antifungal effects of garlic are strongly associated with its sulfur-containing compounds. Allicin is particularly important because of its high chemical reactivity. It can interact with sulfhydryl groups present in proteins and enzymes, potentially disturbing metabolic pathways essential for fungal survival.^[6,7]

Such multi-target chemical reactivity may contribute to antifungal effects that are not easily explained by a single molecular target. However, the biological activity of purified allicin should be distinguished from that of whole garlic oil or other garlic preparations because their chemical compositions differ.

Other garlic-derived sulfur compounds may contribute to antifungal activity, but the mechanisms established for allicin cannot be assigned automatically to a distilled oil. Mechanistic studies should identify the actual test material and measure its chemical composition.^[6,7,21]

3.2 Eugenol and Clove Essential Oil

Eugenol is the major bioactive constituent of clove essential oil and has been extensively investigated for antimicrobial activity. Its lipophilic character facilitates interaction with biological membranes. Experimental and mechanistic studies indicate that eugenol can alter membrane structure and permeability, resulting in leakage of intracellular components and disruption of membrane-associated functions.^[9]

Additional reported effects include interference with cellular metabolism, oxidative balance and microbial developmental processes. In fungi, such multi-target effects may contribute to inhibition of growth and potentially biofilm-associated activity.

3.3 Membrane Disruption and Cellular Leakage

Fungal membranes are essential for maintaining cellular organization and regulating transport. Essential-oil constituents can partition into lipid-rich membrane structures and modify membrane fluidity and permeability. At sufficient concentrations, this may cause leakage of ions and intracellular molecules and impair membrane-associated enzymes.

The membrane-active properties of eugenol provide one plausible explanation for the broad antifungal activity of clove oil. However, the actual mechanism may vary with fungal species, concentration, exposure time and chemical composition of the oil.^[9,10]

3.4 Oxidative Stress and Metabolic Disturbance

Essential oils and their constituents may also disturb cellular redox homeostasis. Garlic-derived sulfur compounds have strong chemical reactivity, whereas eugenol and other phenolic compounds can influence oxidative processes. Such effects may contribute to cellular damage when the fungal antioxidant capacity is exceeded.

Because several mechanisms can occur simultaneously, the antifungal effects of essential oils are best considered multi-target phenomena rather than effects produced by a single pathway.

3.5 Role of Minor Constituents

The biological activity of an essential oil cannot always be predicted solely from its major constituent. Minor components may alter membrane partitioning, chemical stability, permeability and interactions among compounds. Therefore, two clove oils containing similar amounts of eugenol may nevertheless display different biological activities.

This reinforces the importance of chemical characterization and standardized preparation before comparing antifungal studies.

4. Antifungal Activity Against Clinically Relevant Fungal Pathogens

Garlic and clove essential oils have demonstrated in-vitro antifungal activity against several clinically relevant fungi. However, reported activity depends on fungal species and strain, oil

composition, concentration, inoculum, incubation conditions and susceptibility-testing methodology.^[6,9,10]

4.1 Activity of Garlic-Derived Compounds

Allicin has demonstrated antifungal activity, particularly against *Candida albicans*. Its interaction with thiol-containing cellular components provides a plausible biochemical basis for this activity.^[6]

Garlic-derived compounds have also been investigated against dermatophytes and other fungi. However, evidence should be interpreted carefully because studies may use purified compounds, crude extracts, garlic oil or chemically different preparations. Results obtained with purified allicin cannot automatically be extrapolated to an essential-oil formulation.

4.2 Activity of Clove Essential Oil

Clove essential oil has comparatively strong experimental evidence against several fungal groups. Pinto et al. evaluated clove oil against *Candida*, *Aspergillus* and dermatophyte species and demonstrated measurable inhibitory and fungicidal effects.^[10]

The major role of eugenol is supported by mechanistic studies showing antimicrobial effects of eugenol-containing essential oils.^[9] Nevertheless, the complete essential oil may differ from purified eugenol because other constituents can modify biological activity.

4.3 Activity Against Dermatophytes

Dermatophytes are particularly relevant to topical antifungal therapy because infections commonly involve the skin, hair and nails. Clove oil has demonstrated activity against dermatophytes, including *Trichophyton* species.^[10]

The emergence of *T. indotineae* and terbinafine-resistant dermatophytosis highlights the need for new approaches, although essential oils should currently be regarded as investigational rather than established replacements for standard antifungal therapy.^[3]

4.4 Activity Against *Candida* and Moulds

C. albicans and other *Candida* species are important targets for antifungal research. Garlic-derived allicin has demonstrated antifungal activity against *C. albicans*, while clove oil has demonstrated activity against both yeasts and moulds.^[6,10]

The broad activity of clove oil is particularly relevant to topical formulation research, although laboratory activity does not automatically predict clinical effectiveness.

4.5 Limitations of Current Antifungal Evidence

Comparisons among essential-oil studies remain difficult because of differences in oil composition, extraction, dilution method, inoculum size, incubation time and endpoint definition. Agar diffusion is particularly influenced by oil diffusion characteristics and therefore should not be used as the sole basis for comparing antifungal potency.

Future investigations should use standardized oils, clinically relevant isolates, broth microdilution methods, MIC/MFC determination, biofilm models and appropriate controls.

5. Formulation and Evaluation Approaches for Garlic–Clove Essential-Oil Topical Systems

Direct topical application of essential oils is limited by volatility, hydrophobicity, oxidation and potential irritation. Formulation science is therefore essential for translating antifungal activity into a practical topical dosage form.

5.1 Formulation Components and Preparation

A topical garlic–clove formulation may contain the essential oils, surfactants, co-surfactants, aqueous phase, lipid phase, polymers and stabilizers. The ratio of garlic to clove oil should be optimized experimentally rather than selected only on the basis of theoretical synergy.

Nanoemulsions can improve the dispersion of hydrophobic essential oils in aqueous systems. High-energy techniques such as ultrasonication and high-pressure homogenization are commonly used for preparation.^[12]

Lipid-based systems, including solid lipid nanoparticles and nanostructured lipid carriers, provide additional possibilities for incorporating hydrophobic compounds and improving topical delivery.^[13-15]

5.2 Physicochemical Characterization

A formulation should be characterized for particle size, polydispersity index, zeta potential, pH, viscosity, spreadability, loading, release, phase stability and chemical composition. These measurements should be interpreted together because no single parameter establishes product quality.

Dynamic light scattering is commonly used for particle-size and PDI measurements. GC–MS can be used to characterize essential-oil constituents and monitor chemical consistency.

Table 2: Key quality-control and evaluation parameters for garlic–clove essential-oil topical formulations.

Evaluation parameter	Purpose	Recommended/commonly used approach	Refs.
Particle size	Determines dispersion characteristics and influences topical delivery behaviour	Dynamic light scattering (DLS)	[12–15]
Polydispersity index (PDI)	Assesses particle-size distribution and formulation uniformity	DLS-based measurement	[12,13,15]
Zeta potential	Provides information related to colloidal stability	Electrophoretic light scattering	[13,15]
pH	Helps assess dermal compatibility and formulation stability	Calibrated pH measurement	[14,18]
Viscosity	Influences spreadability, residence time and handling properties	Suitable viscometer/rheometer	[14,18]
Chemical composition	Confirms identity and consistency of essential-oil constituents	GC–MS or validated chromatographic profiling	[8,9,11]
Encapsulation/loading efficiency	Determines incorporation of essential-oil constituents into the carrier	Appropriate analytical quantification method	[13–15]
In-vitro release	Evaluates release behaviour of active constituents	Membrane-based or suitable release model	[14,15]
Physical stability	Detects phase separation, aggregation and other instability	Storage studies with periodic physicochemical assessment	[11–15]
Antifungal activity	Determines inhibitory/fungicidal potential	MIC/MFC and appropriate susceptibility-testing methods	[6,10,16]
Skin-retention/permeation	Determines local delivery and potential systemic exposure	Appropriate ex-vivo/in-vitro skin model	[14,15]

5.3 Antifungal Evaluation

Antifungal evaluation should include appropriate reference strains and, where possible, clinical isolates. Broth microdilution is preferable for quantitative determination of MIC, while MFC can provide information regarding fungicidal activity.

For a topical formulation intended for dermatophytosis, relevant organisms may include *Trichophyton rubrum*, *T. mentagrophytes/interdigitale* and, where available, *T. indotineae*. *Candida* species and selected *Aspergillus* species may also be included to investigate broader antifungal activity.

Biofilm assays should be considered because fungal biofilms can exhibit altered susceptibility compared with planktonic cells.

5.4 Stability Evaluation

Essential oils are susceptible to oxidation and other degradation reactions. Heat, light, oxygen and storage conditions can alter their chemical composition and potentially their biological activity.^[11]

Therefore, stability studies should monitor appearance, pH, particle size, PDI, viscosity, phase separation and chemical markers over time. Packaging should minimize exposure to oxygen and light when appropriate.

5.5 Release and Skin-Delivery Evaluation

For a topical formulation, antifungal activity alone is insufficient. The formulation should provide adequate retention at the intended site while minimizing unnecessary systemic exposure.

In-vitro release studies, skin permeation studies and skin-retention experiments can help determine whether the formulation improves local availability of active constituents.

Hydrogels may provide a useful semisolid platform because their three-dimensional polymeric networks can retain large amounts of water and allow incorporation of active compounds.^[14]

6. Synergistic Antifungal Potential of Garlic and Clove Essential Oils

6.1 Rationale for Combination

The oils differ in dominant chemistry: distilled garlic oil contains allyl polysulfides, while clove oil is generally rich in eugenol.^[8,9,21] These differences support investigation of combination effects, but do not establish complementary mechanisms or synergy.

A potential advantage of combination therapy is the possibility of reducing the concentration of each individual component while maintaining antifungal activity. However, this remains a hypothesis until experimentally demonstrated.

6.2 Mechanistic Basis

Eugenol can alter fungal membrane function, while allicin can react with thiol-containing cellular components.^[6,9] For distilled garlic oil, comparable target-level evidence must be established for its measured sulfur constituents before this mechanism is used to explain a combination effect.

If these effects occur simultaneously, the combination could theoretically produce stronger inhibition than either agent alone. However, interactions may also be merely additive, indifferent or even antagonistic.

6.3 Quantitative Evaluation of Synergy

Synergy should be evaluated quantitatively rather than inferred from larger inhibition zones. The checkerboard microdilution method can be used to determine the fractional inhibitory concentration index.

$$FICI = FIC_a + FIC_\beta$$

where

FIC_a = MIC of agent A in combination / MIC of agent A alone

and

FIC_β = MIC of agent B in combination / MIC of agent B alone.

One commonly used convention interprets $FICI \leq 0.5$ as synergy, $>0.5-4$ as no interaction and >4 as antagonism.^[16] Some studies subdivide the intermediate range into additive and indifferent effects. The selected convention, endpoint and assay conditions should be stated in advance, because classifications depend on the method.

Time-kill experiments can provide complementary information by showing whether the combination produces faster or greater fungal killing than the individual components.

6.4 Biofilm-Associated Synergy

Biofilms are particularly important because their physiological characteristics can reduce susceptibility to antimicrobial agents. A garlic-clove formulation should therefore ideally be evaluated against both planktonic cells and established biofilms.

A reduction in biofilm biomass or metabolic activity should be interpreted together with viable-cell measurements to avoid overestimating antifungal effects.

6.5 Future Potential

A standardized garlic–clove combination could potentially provide a broad-spectrum topical system. However, claims of synergy should only be made after quantitative testing.

Future studies should compare different oil ratios, standardized chemical profiles, resistant clinical isolates and biofilm models. Nano-enabled co-delivery could subsequently be investigated to determine whether simultaneous delivery improves antifungal performance.

7. Toxicological Profile, Safety and Clinical Considerations

7.1 Skin Irritation and Sensitization

The therapeutic potential of essential oils must be balanced against dermal safety. Concentrated essential oils may cause irritation, sensitization or cytotoxic effects, particularly when applied to damaged or inflamed skin.

This issue is especially relevant for clove oil because eugenol can exert cytotoxic effects at sufficiently high concentrations. Prashar *et al.* reported cytotoxicity of clove oil and eugenol in human skin-cell models, emphasizing the importance of concentration and formulation.^[17]

Therefore, a formulation should not simply maximize essential-oil concentration. Instead, the antifungal concentration should be compared with the concentration producing undesirable effects in relevant skin-cell models.

7.2 Cytotoxicity Evaluation

Cytotoxicity studies may include human keratinocytes, fibroblasts or other appropriate skin-cell models. The therapeutic window should be determined by comparing antifungal efficacy with cell viability.

A formulation showing strong antifungal activity but substantial cytotoxicity would have limited translational value.

7.3 Dermal Compatibility

Evaluation should include irritation, sensitization and, where appropriate, histopathological assessment in suitable preclinical models. The formulation vehicle itself must also be evaluated because surfactants, solvents and nanoparticles can influence skin compatibility.

Nanoformulation should not automatically be considered safer than conventional formulations. Any improvement in safety must be demonstrated experimentally.

7.4 In-Vivo Evaluation

Before clinical investigation, promising formulations should be evaluated in appropriate animal models of superficial fungal infection. Outcomes may include fungal burden, lesion severity, histopathological changes, inflammatory response and local tolerability.

The in-vivo study should also include a suitable conventional antifungal comparator to determine whether the experimental formulation provides meaningful additional benefit.

7.5 Clinical and Regulatory Considerations

In-vitro antifungal activity does not establish clinical efficacy. Translation requires reproducible manufacturing, chemical standardization, adequate stability, safety data and controlled clinical studies.

Because essential oils can vary substantially between batches, chemical fingerprinting and marker-based quality control should form part of the development strategy.

8. Delivery Platforms and Future Perspectives

8.1 Nanoemulsion-Based Delivery

Nanoemulsions are particularly attractive for essential oils because they can improve the dispersion of lipophilic compounds within an aqueous formulation. Their small droplet size can influence physical stability, interfacial interactions and delivery characteristics.^[12]

For garlic–clove oils, nanoemulsification may reduce some of the practical limitations associated with poor water dispersibility and may provide more uniform dosing.

However, nanoemulsion development requires optimization of surfactant concentration, oil-to-water ratio, energy input and storage conditions.

8.2 Liposomes and Lipid Nanoparticles

Lipid-based systems provide another strategy for delivering poorly water-soluble natural compounds. Solid lipid nanoparticles and nanostructured lipid carriers have been investigated for dermatological and cosmetic applications.^[13]

Lipid nanoparticles have been explored as carriers for natural compounds with formulation limitations.^[15] Such platform evidence supports investigation of garlic–clove delivery, but does not itself establish efficacy or safety for this specific combination.

For garlic–clove oils, these systems could potentially provide controlled local delivery while reducing rapid volatilization.

8.3 Hydrogel and Nano-Hydrogel Systems

Hydrogels are useful topical platforms because their polymeric networks can retain water and provide a semisolid structure suitable for skin application.^[14]

Combining an essential-oil nanoformulation with a hydrogel may provide several advantages, including improved residence time, convenient application and controlled release. Nevertheless, the influence of the polymer network on essential-oil stability and antifungal activity must be evaluated.

8.4 Combination With Conventional Antifungals

An additional research direction is combining garlic or clove constituents with established antifungal drugs. Such combinations may theoretically allow dose reduction or activity against less susceptible strains.

However, combination effects cannot be assumed to be synergistic. Quantitative testing is necessary to identify beneficial combinations and avoid antagonistic interactions.^[16]

8.5 Computational and Omics-Based Approaches

Molecular docking and molecular-dynamics studies can be used to generate hypotheses regarding possible molecular targets. Transcriptomic, proteomic and metabolomic approaches may further clarify cellular responses to garlic and clove constituents.

Nevertheless, computational predictions should be considered hypothesis-generating rather than definitive evidence. Experimental validation remains essential.

8.6 Standardization as a Central Requirement

One of the greatest challenges in essential-oil research is chemical variability. The same botanical species may produce oils with different compositions depending on geography, cultivation, harvesting, extraction and storage.^[11]

Therefore, future garlic–clove formulations should be characterized using validated chemical fingerprints and defined marker compounds. This will improve reproducibility between laboratories and facilitate comparison among studies.

9. Major Knowledge Gaps and Research Priorities

Although garlic and clove essential oils demonstrate promising antifungal properties, several knowledge gaps currently limit their pharmaceutical translation.

9.1 Limited Direct Evidence for Garlic–Clove Combination

Most available evidence concerns garlic-derived compounds or clove/eugenol preparations individually. Direct studies examining standardized garlic–clove essential-oil combinations remain limited.

Future studies should systematically evaluate multiple ratios and determine MIC, MFC, FICI and time-kill profiles.

9.2 Lack of Standardized Essential-Oil Composition

Variability in chemical composition can lead to inconsistent biological results. Each experimental batch should therefore be chemically characterized before biological testing.

9.3 Insufficient Clinical Evidence

Most evidence remains preclinical or laboratory-based. Strong antifungal activity *in vitro* does not necessarily predict therapeutic effectiveness in human skin.

Well-designed clinical studies are required to establish efficacy, optimal dosage, treatment duration and safety.

9.4 Limited Long-Term Safety Information

Short-term cytotoxicity studies provide useful initial information, but repeated topical exposure requires additional assessment. Long-term irritation, sensitization and effects on the skin barrier should be investigated.

9.5 Formulation Stability

Essential-oil volatility and oxidation remain major challenges. Formulation studies should therefore investigate chemical stability together with physical stability.

9.6 Resistant Dermatophytes

The emergence of difficult-to-treat *T. indotineae* highlights the importance of investigating alternative agents against resistant dermatophyte isolates.^[3]

However, laboratory activity against resistant strains should be followed by in-vivo and clinical validation before any therapeutic conclusions are drawn.

9.7 Priority Research Framework

A staged development pathway is presented in Table 3. Initial work should establish chemical identity and individual activity, followed by interaction testing, formulation optimization, safety assessment and translational evaluation.

This stepwise strategy would help distinguish promising experimental observations from evidence suitable for therapeutic translation.

Table 3: Proposed research pathway for development of garlic–clove essential-oil topical antifungal formulations.

Research stage	Major activity	Expected outcome	Refs.
1	Botanical authentication and chemical characterization	Confirmed plant identity and reproducible chemical profile	[8,9,11]
2	Standardization of garlic and clove oils	Defined marker compounds and batch consistency	[7–9,11]
3	Individual MIC/MFC determination	Baseline antifungal activity of each oil	[6,10,16]
4	Optimization of garlic–clove ratios	Identification of potentially effective combinations	[16]
5	Quantitative synergy testing	Classification as synergistic, additive, indifferent or antagonistic	[16]
6	Biofilm evaluation	Assessment of activity against established fungal biofilms	[5,9,10]
7	Cytotoxicity and dermal-safety assessment	Determination of therapeutic window and skin compatibility	[17,18]
8	Nanoformulation development	Determine whether dispersion, stability and topical delivery improve	[12–15,19,20]
9	Stability and release studies	Determination of physical and chemical stability and release behaviour	[11–15]
10	In-vivo antifungal and safety evaluation	Confirmation of efficacy and local tolerability	[14,15,18]

11	Comparative studies with standard antifungal drugs	Assessment of relative therapeutic potential	[4,16]
12	Controlled clinical trials	Establishment of clinical efficacy and safety	[1,3,4]

10. CONCLUSION

Garlic and clove preparations contain compounds with potential relevance to topical antifungal development. Distilled garlic essential oil is characterized mainly by allyl polysulfides, whereas clove oil is typically rich in eugenol.^[8,9,21] Evidence for allicin provides useful mechanistic context but must be interpreted separately from evidence for distilled garlic oil.

Experimental studies provide evidence of antifungal activity against clinically relevant fungi. Garlic-derived allicin has demonstrated activity particularly against *Candida*, while clove essential oil has demonstrated activity against *Candida*, *Aspergillus* and dermatophytes.^[6,10]

The garlic–clove combination is scientifically attractive because its major constituents have different chemical characteristics and potentially complementary mechanisms. Nevertheless, the existence of true synergy cannot be assumed. Quantitative checkerboard studies, FICI analysis, time-kill experiments and biofilm assays are required before claims of synergistic activity can be made.^[16]

Nanoemulsions, lipid nanoparticles and hydrogels offer possible approaches to dispersion, stability and local delivery.^[12-15] Much of the cited formulation literature concerns general platforms, and reference.^[12] concerns food applications. Benefits for a topical garlic–clove product therefore require direct comparative evaluation.

Safety is equally important. Essential oils can produce irritation and cytotoxicity at sufficiently high concentrations. In particular, clove oil and eugenol have demonstrated cytotoxic effects in human skin-cell models, highlighting the importance of concentration optimization and dermal compatibility testing.^[17]

The major research priorities are therefore chemical standardization, optimization of garlic–clove ratios, quantitative synergy testing, resistant dermatophyte evaluation, biofilm studies, nano-enabled co-delivery, long-term dermal-safety assessment, in-vivo validation and controlled clinical trials.

Overall, garlic–clove essential-oil formulations provide a promising research interface between natural-product pharmacology and advanced topical drug delivery. Their potential should, however, be described as promising but investigational until reproducible formulations, adequate safety profiles and clinical efficacy have been established.

REFERENCES

1. World Health Organization. (2022). WHO fungal priority pathogens list to guide research, development and public health action. World Health Organization.
2. Bongomin, F., Gago, S., Oladele, R. O., & Denning, D. W. (2017). Global and multi-national prevalence of fungal diseases—Estimate precision. *Journal of Fungi*, 3(4): 57. <https://doi.org/10.3390/jof3040057>
3. Chowdhary, A., Singh, A., Kaur, A., & Khurana, A. (2022). The emergence and worldwide spread of the species *Trichophyton indotineae* causing difficult-to-treat dermatophytosis: A new challenge in the management of dermatophytosis. *PLoS Pathogens*, 18(9): e1010795. <https://doi.org/10.1371/journal.ppat.1010795>
4. Pappas, P. G., Kauffman, C. A., Andes, D. R., Clancy, C. J., Marr, K. A., Ostrosky-Zeichner, L., Reboli, A. C., Schuster, M. G., Vazquez, J. A., Walsh, T. J., Zaoutis, T. E., & Sobel, J. D. (2016). Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, 62(4): e1–e50. <https://doi.org/10.1093/cid/civ933>
5. Swamy, M. K., Akhtar, M. S., & Sinniah, U. R. (2016). Antimicrobial properties of plant essential oils against human pathogens and their mode of action: An updated review. *Evidence-Based Complementary and Alternative Medicine*, 2016; 3012462. <https://doi.org/10.1155/2016/3012462>
6. Ankri, S., & Mirelman, D. (1999). Antimicrobial properties of allicin from garlic. *Microbes and Infection*, 1(2): 125–129. [https://doi.org/10.1016/S1286-4579\(99\)80003-3](https://doi.org/10.1016/S1286-4579(99)80003-3)
7. Borlinghaus, J., Albrecht, F., Gruhlke, M. C. H., Nwachukwu, I. D., & Slusarenko, A. J. (2014). Allicin: Chemistry and biological properties. *Molecules*, 19(8): 12591–12618. <https://doi.org/10.3390/molecules190812591>
8. Cortés-Rojas, D. F., de Souza, C. R. F., & Oliveira, W. P. (2014). Clove (*Syzygium aromaticum*): A precious spice. *Asian Pacific Journal of Tropical Biomedicine*, 4(2): 90–96. [https://doi.org/10.1016/S2221-1691\(14\)60215-X](https://doi.org/10.1016/S2221-1691(14)60215-X)
9. Marchese, A., Barbieri, R., Coppo, E., Orhan, I. E., Daglia, M., Nabavi, S. F., Izadi, M., Abdollahi, M., Nabavi, S. M., & Ajami, M. (2017). Antimicrobial activity of eugenol and

- essential oils containing eugenol: A mechanistic viewpoint. *Critical Reviews in Microbiology*, 43(6): 668–689. <https://doi.org/10.1080/1040841X.2017.1295225>
10. Pinto, E., Vale-Silva, L., Cavaleiro, C., & Salgueiro, L. (2009). Antifungal activity of the clove essential oil from *Syzygium aromaticum* on *Candida*, *Aspergillus* and dermatophyte species. *Journal of Medical Microbiology*, 58(11): 1454–1462. <https://doi.org/10.1099/jmm.0.010538-0>
11. Turek, C., & Stintzing, F. C. (2013). Stability of essential oils: A review. *Comprehensive Reviews in Food Science and Food Safety*, 12(1): 40–53. <https://doi.org/10.1111/1541-4337.12006>
12. Donsì, F., & Ferrari, G. (2016). Essential oil nanoemulsions as antimicrobial agents in food. *Journal of Biotechnology*, 233, 106–120. <https://doi.org/10.1016/j.jbiotec.2016.07.005>
13. Müller, R. H., Radtke, M., & Wissing, S. A. (2002). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Advanced Drug Delivery Reviews*, 54(Suppl. 1): S131–S155. [https://doi.org/10.1016/S0169-409X\(02\)00118-7](https://doi.org/10.1016/S0169-409X(02)00118-7)
14. Ahmed, E. M. (2015). Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research*, 6(2): 105–121. <https://doi.org/10.1016/j.jare.2013.07.006>
15. Puglia, C., Pignatello, R., Fuochi, V., Furneri, P. M., Lauro, M. R., Santonocito, D., Cortesi, R., & Esposito, E. (2019). Lipid nanoparticles and active natural compounds: A perfect combination for pharmaceutical applications. *Current Medicinal Chemistry*, 26(24): 4681–4696. <https://doi.org/10.2174/0929867326666190614123835>
16. Odds, F. C. (2003). Synergy, antagonism, and what the checkerboard puts between them. *Journal of Antimicrobial Chemotherapy*, 52(1): 1. <https://doi.org/10.1093/jac/dkg301>
17. Prashar, A., Locke, I. C., & Evans, C. S. (2006). Cytotoxicity of clove (*Syzygium aromaticum*) oil and its major components to human skin cells. *Cell Proliferation*, 39(4): 241–248. <https://doi.org/10.1111/j.1365-2184.2006.00384.x>
18. Ribeiro, A. S., Estanqueiro, M., Oliveira, M. B., & Lobo, J. M. S. (2015). Main benefits and applicability of plant extracts in skin care products. *Cosmetics*, 2(2): 48–65. <https://doi.org/10.3390/cosmetics2020048>
19. McClements, D. J. (2012). Nanoemulsions versus microemulsions: Terminology, differences, and similarities. *Soft Matter*, 8: 1719–1729. <https://doi.org/10.1039/C2SM06903B>

20. Müller, R. H., Mäder, K., & Gohla, S. (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery—A review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1): 161–177. [https://doi.org/10.1016/S0939-6411\(00\)00087-4](https://doi.org/10.1016/S0939-6411(00)00087-4)
21. Satyal, P., Craft, J. D., Dosoky, N. S., & Setzer, W. N. (2017). The chemical compositions of the volatile oils of garlic (*Allium sativum*) and wild garlic (*Allium vineale*). *Foods*, 6(8): 63. <https://doi.org/10.3390/foods6080063>