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Synthetic and Herbal Oil-Based Topical Creams for Antifungal Therapy: A Comprehensive Review

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Abstract

Superficial fungal infections remain a major global public-health burden, driven by high prevalence, recurrence, and rising resistance to standard agents. This comprehensive review examines contemporary topical antifungal creams that combine synthetic drugs (azoles, allylamines, polyenes) with herbal oil-based excipients and actives (for example, neem, tea tree oil, coconut oil, silymarin). We synthesize evidence from in-vitro studies, formulation research, clinical trials, and quality-control reports to compare antifungal efficacy, mechanisms of action, skin-penetration strategies, and safety profiles. The review highlights how herbal oils can serve dual roles as bioactive adjuncts providing intrinsic antifungal, anti-inflammatory, or wound-healing effects and as formulation vehicles that modify solubility, enhance dermal delivery, and reduce irritation. We discuss formulation challenges including batch variability of botanical extracts, compatibility with synthetic actives, stability, and regulatory considerations for hybrid products. Emerging technologies such as lipid-based nanocarriers, microemulsions, and penetration enhancers are evaluated for their potential to improve therapeutic outcomes and reduce dosing frequency. Finally, we identify gaps in the literature notably limited large-scale randomized trials on combination formulations and inconsistent standardization of herbal constituents and recommend priorities for future research, including standardized phytochemical profiling, head-to-head clinical comparisons, and safety monitoring frameworks. This review aims to inform formulators, clinicians, and regulatory stakeholders about the opportunities and limitations of synthetic–herbal topical antifungal therapies.

1.INTRODUCTION

Superficial fungal infections are among the most common dermatological conditions, affecting millions worldwide and posing significant therapeutic challenges. Conventional antifungal treatments, particularly synthetic agents such as azoles and allylamines, remain the mainstay of therapy due to their proven efficacy [1]. However, issues like drug resistance, side effects, and prolonged treatment duration have prompted growing interest in alternative or complementary approaches. Herbal oils, including neem, tea tree, coconut, and babchi oil, possess well-documented antifungal, anti-inflammatory, and skin-protective properties, making them promising candidates for topical therapy [2-5]. Recent advances in formulation science have focused on combining synthetic drugs with herbal oils in cream bases to achieve synergistic effects, enhance skin penetration, and improve patient compliance. This comprehensive review highlights the role of synthetic antifungal agents, the antifungal potential of herbal oils, formulation strategies, evaluation parameters, and future perspectives in the development of synthetic–herbal oil-based topical creams for effective antifungal therapy [6-8].

Burden of Fungal Infections

Fungal infections constitute one of the most widespread health challenges globally, affecting both developed and developing nations. They can be classified broadly into superficial, subcutaneous, and systemic infections. Superficial fungal infections, particularly dermatophytosis (ringworm), candidiasis, and pityriasis versicolor, are the most common, impacting the skin, hair, and nails. According to the World Health Organization, superficial fungal infections affect 20–25% of the global population at any given time, making them a major dermatological burden [9-11]. The prevalence is higher in tropical and subtropical regions such as India, Southeast Asia, and parts of Africa due to warm, humid climates that favor fungal growth. Factors such as poor personal hygiene, occlusive clothing, prolonged antibiotic use, and immunosuppression (e.g., in HIV/AIDS, organ transplant recipients, or cancer patients undergoing chemotherapy) further increase susceptibility. In addition to high prevalence, fungal infections cause significant morbidity, including itching, inflammation, pain, and cosmetic disfigurement. Although not life-threatening in most cases, they contribute to psychological distress, social stigma, and reduced quality of life [12, 13]. Moreover, recurrent or chronic fungal infections lead to persistent treatment needs, creating an economic burden on healthcare systems. The global antifungal market continues to expand due to rising incidence and increasing

antifungal resistance, highlighting the urgency of new, effective therapeutic strategies [14-16].

Need for Effective Topical Antifungal Therapies

Topical antifungal therapy is the cornerstone of treatment for superficial infections. Unlike systemic antifungals, which circulate throughout the body, topical formulations deliver the drug directly to the site of infection, thereby minimizing systemic toxicity and drug–drug interactions. Creams, ointments, gels, and sprays are widely prescribed due to their ease of use, patient compliance, and ability to act locally [17-19].

However, several limitations exist with current topical antifungal formulations:

- **Limited skin penetration**: The stratum corneum acts as a major barrier, reducing drug permeation to deeper layers of skin where fungi often reside [20].
- **Short residence time**: Creams or gels may be removed due to sweating, washing, or friction, leading to poor retention and frequent reapplication [21].
- **Resistance development**: Repeated exposure to antifungal drugs, particularly azoles, has contributed to the emergence of resistant strains of *Candida* and dermatophytes [22].
- **Recurrence of infections**: Even after apparent clinical cure, incomplete eradication often leads to relapse [23].

To overcome these drawbacks, researchers are exploring novel delivery systems such as nanoemulsions, liposomes, cubosomes, and transdermal nanocarriers. These systems enhance solubility, improve skin penetration, and provide sustained release. At the same time, interest has grown in incorporating natural oils with antifungal and anti-inflammatory properties into topical bases to enhance therapeutic outcomes [24-26].

Role of Synthetic Drugs and Herbal Oils

Synthetic Antifungal Drugs

Synthetic antifungals remain the primary therapeutic option for fungal infections due to their defined chemical structure, predictable pharmacological activity, and high potency. Among them, azole derivatives (e.g., clotrimazole, ketoconazole, luliconazole, itraconazole) are most widely used [27, 28]. They act by inhibiting lanosterol 14α-demethylase, a key enzyme in ergosterol biosynthesis, which is essential for maintaining fungal cell membrane integrity. The disruption of ergosterol synthesis leads to increased membrane permeability and eventual cell death [29-31].

Other important classes include:

- **Allylamines** (e.g., terbinafine, naftifine) – inhibit squalene epoxidase, another key enzyme in ergosterol biosynthesis.
- **Polyenes** (e.g., nystatin, amphotericin B) – bind directly to ergosterol, creating pores in the fungal cell membrane.
- **Echinocandins** (used systemically) – inhibit β-glucan synthesis, compromising fungal cell wall integrity.

Despite their effectiveness, synthetic drugs have limitations such as local irritation, allergic reactions, and resistance. For example, luliconazole, a potent imidazole antifungal, is effective against dermatophytes but requires careful formulation to achieve adequate skin penetration without irritation [32-34].

Herbal Oils

Herbal oils have been used for centuries in traditional medicine to manage skin ailments, including fungal infections. These oils are rich in bioactive phytoconstituents that exhibit antifungal, anti-inflammatory, antioxidant, and wound-healing properties [35]. Examples include:

- **Babchi oil (Psoralea corylifolia):** Contains psoralen and bakuchiol, known for antifungal, antibacterial, and skin-regenerating effects.
- **Neem oil (Azadirachta indica):** Rich in azadirachtin and nimbidin, with broad-spectrum antimicrobial activity.
- **Tea tree oil (Melaleuca alternifolia):** Contains terpinen-4-ol, an effective antifungal and antibacterial compound.
- **Coconut oil:** Provides lauric acid, with antifungal and soothing skin effects.

These oils act via multiple mechanisms, such as disrupting fungal cell membranes, inhibiting spore germination, and modulating host immune responses. Unlike synthetic drugs, herbal oils have a lower risk of resistance development due to their multi-targeted action [36-40].

Synthetic-Herbal Combination Therapy

The integration of synthetic drugs with herbal oils in topical formulations has emerged as a promising strategy. This synergistic approach offers several advantages:

- Enhanced antifungal efficacy through complementary mechanisms.
- Reduced required dose of synthetic drug, thereby lowering side effects.
- Potential to overcome resistance by multi-target action.
- Added benefits such as skin hydration, wound healing, and anti-inflammatory effects from herbal oils [41, 42].

For instance, a luliconazole–babchi oil topical cream may provide rapid fungal clearance due to the potent azole mechanism of luliconazole combined with the natural antifungal and skin-regenerating effects of babchi oil. Such hybrid formulations represent the next generation of antifungal therapies that integrate modern pharmacology with traditional phytotherapy [43-45].

2. Overview of Topical Antifungal Therapy

Importance of Localized Drug Delivery

Superficial fungal infections such as dermatophytosis, candidiasis, and pityriasis versicolor are among the most common skin disorders globally, affecting millions of people each year. These infections are generally confined to the stratum corneum, hair shafts, and nails, making them accessible to treatment with localized drug delivery systems [46]. Topical antifungal therapy has therefore become the first-line approach for uncomplicated superficial infections due to its ability to provide effective drug concentrations directly at the site of infection. Localized delivery ensures that the antifungal agent penetrates into the epidermis, dermis, and adnexal structures where fungi reside, while minimizing systemic exposure. This site-specific drug release not only enhances therapeutic outcomes but also reduces the risk of systemic adverse effects such as hepatotoxicity, nephrotoxicity, or gastrointestinal disturbances, which are commonly associated with oral antifungal agents [47-50].

Another important advantage is the rapid relief of symptoms such as itching, burning, and scaling, which greatly improves patient satisfaction and compliance. In addition, topical formulations can be designed to sustain drug release, improve skin permeation, and target fungal biofilms, which are increasingly recognized as contributors to chronic or recurrent infections. Recent

advancements in localized antifungal delivery include nanoformulations such as liposomes, niosomes, cubosomes, solid lipid nanoparticles, and nanoemulsions. These systems not only improve solubility and stability of poorly water-soluble antifungals (e.g., azoles, allylamines) but also facilitate penetration into deeper skin layers and nails, where conventional formulations often fail. Thus, localized topical therapy represents a safe, effective, and patient-friendly strategy in the management of fungal skin infections [51-55].

Limitations of Oral/Systemic Antifungals

Although systemic antifungals are indispensable for severe, widespread, or resistant fungal infections, their clinical use is constrained by multiple drawbacks. Oral antifungals such as fluconazole, itraconazole, terbinafine, and griseofulvin are effective but require long treatment courses, particularly in onychomycosis (nail infections), where therapy may extend from several weeks to months. One of the major concerns with systemic antifungal therapy is toxicity. Azoles are associated with hepatotoxicity due to their metabolism through the cytochrome P450 pathway, and terbinafine has been linked to hepatobiliary dysfunction. Amphotericin B, though rarely used topically, is notorious for its nephrotoxicity when administered systemically. Patients on prolonged therapy must undergo regular liver and kidney function monitoring, which adds to treatment costs and complexity [56].

Another limitation is the high potential for drug–drug interactions. Azoles inhibit cytochrome P450 enzymes, leading to elevated levels of co-administered drugs such as statins, anticoagulants, or immunosuppressants, thereby increasing the risk of adverse events. Additionally, systemic antifungals may cause gastrointestinal side effects such as nausea, vomiting, diarrhea, and abdominal discomfort, reducing patient adherence. Poor compliance is a major reason for treatment failure and relapse in fungal infections. Moreover, with prolonged systemic therapy, there is an increasing risk of antifungal resistance. Fungi such as *Candida* and *Aspergillus* species have developed resistance mechanisms including efflux pump overexpression and target enzyme modification, making systemic agents less effective over time. Thus, while systemic antifungals remain essential for severe infections, their limitations highlight the need for effective topical formulations for mild to moderate superficial infections [57-59].

Advantages of Topical Creams [60-63]

Topical antifungal creams offer several distinct advantages over systemic therapy, making them the preferred choice for localized infections such as athlete's foot, ringworm, jock itch, and cutaneous candidiasis.

a. Direct Drug Delivery at the Site of Infection
Topical creams deliver the drug precisely to the infected area, ensuring maximum local concentration with minimal systemic absorption. This direct action leads to rapid reduction in fungal burden and quicker symptom relief.

b. Reduced Systemic Toxicity
Since absorption into systemic circulation is negligible; the risk of systemic adverse effects such as hepatotoxicity or nephrotoxicity is minimal. This makes topical therapy especially safe for children, elderly patients, and those with comorbidities.

c. Patient-Friendly and Versatile Formulations
Antifungal creams are available in multiple dosage forms—creams, ointments, gels, sprays, and lotions—allowing flexibility according to infection site and patient preference. For example, creams are commonly used for moist areas like groin folds, while gels and sprays are convenient for hairy regions like the scalp.

d. Improved Compliance and Cost-Effectiveness
Topical formulations are generally affordable, easily accessible over the counter, and simple to apply, improving patient adherence. Shorter treatment durations and rapid symptom relief further enhance compliance.

e. Scope for Novel and Combination Therapies
Modern research has enabled the development of advanced topical drug delivery systems such as liposomal gels, nanoemulsions, and cubosomal creams, which enhance drug solubility and skin penetration. Furthermore, combination formulations incorporating both synthetic antifungals and herbal oils (e.g., neem, tea tree oil, coconut oil) have shown synergistic effects, improved antifungal efficacy, and added anti-inflammatory or wound-healing benefits.

f. Suitability for Mild to Moderate Infections
For localized superficial fungal infections, topical therapy is usually sufficient to achieve complete cure without the risks associated with oral therapy. Only in extensive or refractory cases is systemic therapy required, often in combination with topical agents for improved outcomes.

Synthetic Antifungal Agents in Cream Formulations

Topical antifungal therapy plays a crucial role in the management of superficial fungal infections, offering localized treatment with minimal systemic side effects. Among topical options, synthetic antifungal agents have remained the cornerstone due to their well-established efficacy, reproducibility, and broad-spectrum activity against dermatophytes, yeasts, and certain molds. These agents are incorporated into cream formulations to ensure optimal drug delivery, enhanced patient compliance, and convenient application [64-66]. The most commonly used classes of synthetic antifungals in topical creams include azoles, allylamines, benzylamines, and a few other specialized agents such as ciclopirox, tolnaftate, and amorolfine. Each class exhibits a distinct mechanism of action, primarily targeting fungal cell membrane integrity or key enzymatic pathways involved in ergosterol biosynthesis, thereby inhibiting fungal growth or inducing cell death. Over the years, numerous synthetic antifungal creams have been developed and marketed, varying in potency, spectrum, and formulation properties to meet specific clinical needs. Understanding the types, mechanisms, and marketed examples of synthetic antifungal agents is essential for designing effective topical therapies and for optimizing combination approaches with herbal actives for enhanced antifungal efficacy [67-69].

1. Common Synthetic Antifungals in Cream Formulations

Topical antifungal creams predominantly contain synthetic agents belonging to a few well-established drug classes, most notably azoles and allylamines. These agents are considered first-line therapy for superficial mycoses, including dermatophytosis (*tinea* infections), cutaneous candidiasis, and pityriasis versicolor [70].

- **Azoles (Imidazoles and Triazoles):**
  - Widely used in topical formulations.
  - Include clotrimazole, miconazole, ketoconazole, econazole, luliconazole, and sertaconazole.
  - Preferred due to their broad-spectrum activity against dermatophytes, yeasts (*Candida spp.*), and some molds [71].
- **Allylamines and Benzylamines:**
  - Include terbinafine, naftifine, and butenafine.
  - Highly effective against dermatophytes due to their potent inhibition of ergosterol biosynthesis.
  - Often require shorter treatment courses compared to azoles [72].

- **Other Synthetic Antifungals:**
  - **Ciclopirox olamine:** Broad-spectrum agent effective against fungi and some bacteria, often used in nail and skin formulations.
  - **Tolnaftate:** Commonly used in over-the-counter creams for athlete's foot and ringworm.
  - **Amorolfine:** Used in topical and nail formulations with fungistatic and fungicidal activity [73].

Together, these synthetic antifungal agents constitute the majority of marketed cream formulations due to their proven efficacy, safety, and patient compliance.

2. Mechanism of Action of Synthetic Antifungals

The antifungal activity of synthetic drugs largely revolves around the disruption of ergosterol synthesis, a vital component of fungal cell membranes.

- **Azoles (e.g., clotrimazole, ketoconazole, luliconazole):**
  - Inhibit the enzyme lanosterol 14-α-demethylase, a cytochrome P450-dependent enzyme in the ergosterol biosynthesis pathway.
  - This leads to depletion of ergosterol and accumulation of toxic sterol intermediates, compromising membrane integrity and inhibiting fungal growth.
  - Exhibit fungistatic activity, though some (e.g., luliconazole) can be fungicidal at higher concentrations [74].
- **Allylamines (e.g., terbinafine, naftifine):**
  - Inhibit the enzyme squalene epoxidase, an earlier step in ergosterol biosynthesis.
  - This results in the accumulation of squalene, which is toxic to fungal cells, and depletion of ergosterol.
  - Strongly fungicidal against dermatophytes, making them highly effective in shorter treatment durations [75].
- **Ciclopirox:**
  - Acts via chelation of polyvalent cations (Fe^{3+}, Al^{3+}), leading to inhibition of metal-dependent enzymes required for cellular energy metabolism and nutrient transport.
  - Unlike azoles/allylamines, its mechanism is non-ergosterol dependent [76].
- **Tolnaftate:**
  - Mechanism not fully elucidated, but believed to distort hyphae and inhibit squalene epoxidase to some extent.

Thus, synthetic antifungal creams primarily act by weakening fungal cell membranes or interfering with vital enzyme functions, leading to impaired growth and eventual cell death.

3. Examples of Marketed Formulations [77]

A wide range of topical antifungal creams containing synthetic agents are commercially available and widely prescribed. Some notable marketed formulations include:

- **Azole-based creams:**
  - *Clotrimazole 1% cream* (Canesten®, Lotrimin®) – Broad-spectrum antifungal for dermatophytes and yeasts.
  - *Ketoconazole 2% cream* (Nizoral®) – Effective in seborrheic dermatitis, candidiasis, and dermatophytosis.
  - *Econazole 1% cream* (Spectazole®) – Used for ringworm and cutaneous candidiasis.
  - *Luliconazole 1% cream* (Luzu®) – A newer azole with superior potency and short treatment duration.
  - *Sertaconazole 2% cream* (Ertaczo®) – Exhibits antifungal and anti-inflammatory effects.
- **Allylamine and benzylamine creams:**
  - *Terbinafine 1% cream* (Lamisil®) – Rapid fungicidal activity, often requiring only 1–2 weeks of therapy.
  - *Naftifine 1% cream/gel* (Naftin®) – Broad-spectrum, also has anti-inflammatory effects.
  - *Butenafine 1% cream* (Lotrimin Ultra®) – Fungicidal activity with improved skin penetration.
- **Other synthetic antifungals:**
  - *Ciclopirox olamine 1% cream* (Loprox®) – Effective in dermatomycoses, seborrheic dermatitis, and candidiasis.
  - *Tolnaftate 1% cream* (Tinactin®) – Widely available OTC product for athlete's foot and ringworm.
  - *Amorolfine cream/nail lacquer* – Effective against dermatophytes and yeast, mostly used for nail infections.

These formulations differ in spectrum of activity, potency, treatment duration, and patient suitability, allowing clinicians to tailor therapy according to infection type and severity.

4. Herbal Oils with Antifungal Potential

Herbal oils have been widely used in traditional medicine systems such as Ayurveda, Unani, and Traditional Chinese Medicine for managing skin disorders, including fungal infections. With growing concerns about antifungal resistance, systemic toxicity, and limited penetration of synthetic drugs, herbal oils are gaining attention as natural, safe, and effective alternatives or adjuncts in antifungal therapy. Many of these oils contain bioactive phytoconstituents with fungistatic and fungicidal activities, acting through mechanisms distinct from synthetic antifungals [78].

Below, some key herbal oils with proven antifungal potential are discussed.

a. Babchi Oil (*Psoralea corylifolia*)

- **Traditional Use:** Babchi oil has long been used in Ayurveda for the treatment of skin conditions such as vitiligo, leprosy, eczema, and fungal infections.
- **Phytoconstituents:** Major active compounds include psoralen, isopsoralen, bakuchiol, bavachinin, bavachin, corylifolin, and corylin.
- **Mechanism of Action:**
  - Psoralen and related furanocoumarins exhibit phototoxic activity, which enhances their antifungal potential upon UV exposure.
  - Bakuchiol, a meroterpene phenol, demonstrates strong antifungal activity by disrupting fungal cell membrane integrity and inhibiting ergosterol biosynthesis.

- Studies have shown that babchi oil is effective against Candida spp., Trichophyton spp., and Aspergillus spp., making it useful in dermatophytic and yeast infections.

- **Applications:** Often formulated into topical creams, ointments, or blended with other herbal oils for management of ringworm, athlete's foot, and candidiasis [79].

b. Neem Oil (*Azadirachta indica*)

- **Traditional Use:** Neem has been regarded as a "universal healer" in Ayurveda, with its oil commonly used for skin infections, ulcers, and wounds.

- **Phytoconstituents:** Contains azadirachtin, nimbidin, nimbin, nimbolide, gedunin, salannin, and fatty acids.

- **Mechanism of Action:**
  - Neem oil demonstrates broad-spectrum antifungal activity, primarily through inhibition of spore germination and mycelial growth.
  - Active limonoids (nimbidin, azadirachtin) disrupt fungal cell wall synthesis and inhibit hyphal development.
  - Exhibits significant efficacy against Candida albicans, Trichophyton rubrum, and Microsporum spp.

- **Applications:** Neem oil is used in antifungal creams, shampoos, and soaps. Its anti-inflammatory and wound-healing properties make it especially suitable for treating cutaneous fungal infections associated with irritation [80].

c. Tea Tree Oil (*Melaleuca alternifolia*)

- **Traditional Use:** Widely used in Australian aboriginal medicine for infections and wound care.

- **Phytoconstituents:** Rich in terpinen-4-ol, α-terpineol, cineole, γ-terpinene, and α-pinene.

- **Mechanism of Action:**
  - The main component, terpinen-4-ol, disrupts fungal cell membrane integrity by altering permeability, leading to leakage of cellular contents.
  - Tea tree oil exhibits fungicidal activity against Candida spp., dermatophytes, and Malassezia spp.
  - It can also disrupt fungal biofilms, a major cause of recurrent infections.

- **Applications:** Incorporated in creams, gels, nail lacquers, and shampoos, particularly for onychomycosis, dandruff, and skin fungal infections [81].

d. Coconut Oil (*Cocos nucifera*)

- **Traditional Use:** Commonly used in tropical regions for skin and hair care; valued for its antimicrobial and soothing effects.

- **Phytoconstituents:** Contains medium-chain fatty acids (MCFAs) such as lauric acid, caprylic acid, capric acid, and monolaurin.

- **Mechanism of Action:**
  - Lauric acid and monolaurin exert potent antifungal activity by disrupting the lipid bilayer of fungal cell membranes.
  - Caprylic acid interferes with mitochondrial energy metabolism in fungi.
  - Coconut oil is particularly effective against Candida albicans, making it useful for both cutaneous and mucocutaneous candidiasis.

- **Applications:** Used alone or as base oil in antifungal herbal creams, ointments, and hair oils. It also improves skin hydration, reducing itching and dryness associated with fungal infections [82].

e. Other Herbal Oils with Antifungal Potential [83]

- **Castor Oil (*Ricinus communis*):** Contains ricinoleic acid with activity against dermatophytes and yeasts.

- **Clove Oil (*Syzygium aromaticum*):** Rich in eugenol, which inhibits ergosterol biosynthesis and fungal hyphal growth.

- **Oregano Oil (*Origanum vulgare*):** Contains carvacrol and thymol, disrupting fungal membranes and inhibiting spore germination.

- **Eucalyptus Oil (*Eucalyptus globulus*):** Exhibits antifungal effects via 1,8-cineole and limonene.

5. Synthetic-Herbal Oil-Based Topical Creams

Superficial fungal infections, caused by dermatophytes, *Candida*, and *Malassezia* species, represent a significant global health concern. While synthetic antifungal agents such as azoles and allylamines remain the gold standard, they are not without limitations prolonged treatment duration, adverse effects, and resistance development. On the other hand, herbal oils like neem, tea tree, coconut, and babchi have long been used in traditional medicine for their broad-spectrum antimicrobial and skin-healing properties.

The concept of synthetic–herbal combination creams merges the potency and selectivity of synthetic antifungals with the multi-targeted, natural activity of herbal oils, creating a synergistic approach that enhances efficacy while improving tolerability and patient compliance [84].

1. Rationale for Combining Synthetic and Herbal Agents

The combination of synthetic and herbal components in topical antifungal creams is scientifically justified due to several complementary benefits:

- **Enhanced Antifungal Efficacy:**
  - Synthetic drugs typically inhibit a specific enzyme in ergosterol biosynthesis, while herbal oils contain terpenes, phenols, and fatty acids that disrupt fungal membranes, inhibit spore germination, or act on biofilms.
  - This multi-targeted action enhances fungicidal potential and reduces relapse [85-86].

- **Reduction in Drug Resistance:**
  - Herbal oils, with multiple active compounds, make it harder for fungi to adapt and develop resistance.
  - Combination therapy reduces the required dose of synthetic antifungal, thereby minimizing selection pressure for resistant strains [87-89].

- **Improved Skin Penetration:**

- Terpenes present in tea tree, eucalyptus, and clove oil act as natural penetration enhancers, improving delivery of synthetic drugs across the stratum corneum [90].

- **Added Therapeutic Benefits:**
  - Herbal oils often provide anti-inflammatory, antioxidant, and wound-healing properties, reducing irritation, redness, and itching.
  - Coconut oil, for example, hydrates the skin and restores barrier function [91].

- **Patient Acceptance:**
  - The "natural" component of these formulations often improves compliance, particularly in populations that trust herbal or traditional remedies [92].

2. Reported Synergistic Effects [93-95]

Several studies have demonstrated that combining synthetic antifungals with herbal oils results in synergistic or additive antifungal effects:

- **Clotrimazole + Tea Tree Oil:** Enhanced inhibition of *Candida albicans* and dermatophytes, with faster fungicidal activity.
- **Ketoconazole + Neem Oil:** Showed improved efficacy against *Trichophyton rubrum* and *Microsporum canis*, due to neem's limonoids interfering with fungal growth.
- **Luliconazole + Babchi Oil (Psoralea corylifolia):** Bakuchiol in babchi oil enhances membrane disruption, complementing luliconazole's ergosterol pathway inhibition.
- **Terbinafine + Coconut Oil:** Medium-chain fatty acids destabilize fungal membranes and enhance terbinafine uptake, reducing treatment time.
- **Ciclopirox + Clove Oil:** Reported synergistic inhibition of resistant *Candida* strains due to eugenol's fungicidal action.

These findings indicate that **synthetic-herbal combinations not only improve antifungal potency but may also shorten treatment duration and reduce recurrence rates**.

3. Case Studies from Literature [96-98]

Evidence from clinical trials, case reports, and patents highlights the practical value of these hybrid formulations:

- **Clotrimazole + Neem/Turmeric Oil Cream:**
  - A randomized clinical study in dermatophytosis patients reported higher cure rates and faster symptom relief compared to clotrimazole alone.
  - Neem provided antifungal and anti-inflammatory action, while turmeric enhanced wound healing.
- **Terbinafine + Coconut Oil (Tinea Pedis):**
  - Patients treated with the combination cream achieved complete cure within 2 weeks, compared to 3–4 weeks for terbinafine alone.
  - Coconut oil's fatty acids improved skin hydration and penetration.
- **Ketoconazole + Tea Tree Oil:**
  - Clinical case reports in cutaneous candidiasis showed faster lesion resolution and reduced itching compared to ketoconazole monotherapy.
  - Tea tree oil also reduced inflammatory symptoms.
- **Sertaconazole + Babchi Oil in Psoriasis with Secondary Fungal Infection:**
  - Case studies demonstrated dual benefits—fungal clearance and improvement in psoriatic lesions, owing to bakuchiol's antifungal and anti-inflammatory effects.
- **Patent Literature and Marketed Formulations:**
  - Several patents describe formulations combining azoles with neem, tea tree, or aloe vera oil.
  - In India and Southeast Asia, polyherbal antifungal creams containing clotrimazole with neem or coconut oil are commercially marketed, although systematic trials are still limited.

6. Formulation Strategies for Antifungal Creams

Topical antifungal creams are the mainstay of therapy for superficial fungal infections because of their localized action, patient-friendly use, and reduced systemic toxicity. However, the success of these creams is not only determined by the active antifungal drug but also by the formulation design including the type of base, excipients, penetration enhancers, and overall stability of the product. An optimized formulation must ensure effective drug delivery to the site of infection, adequate residence time, and long-term stability without compromising patient acceptability [96-99].

1. Cream Bases (O/W, W/O, Emulsion Systems)

Creams are semisolid emulsions composed of oil and water phases stabilized by emulsifiers. The choice of emulsion system strongly influences drug release, skin penetration, and patient compliance [100-103].

- **Oil-in-Water (O/W) Creams:**
  - Oil droplets are dispersed in a continuous aqueous phase.
  - Preferred for non-greasy, washable, and cosmetically elegant formulations.
  - Better patient compliance due to easy spreadability and rapid absorption.
  - Suitable for infections in moist areas (e.g., groin, armpits).
  - Commonly used for azole creams (clotrimazole, ketoconazole) [104].
- **Water-in-Oil (W/O) Creams:**
  - Water droplets dispersed in a continuous oily phase.
  - Provide occlusive and emollient effects, enhancing drug retention and penetration through the stratum corneum.
  - Better suited for dry, scaly fungal infections or for drugs requiring deep penetration.
  - Common in terbinafine or butenafine creams, where occlusion aids fungicidal activity [105].
- **Multiple/Complex Emulsion Systems:**
  - O/W/O or W/O/W emulsions are increasingly studied to improve drug loading, stability, and controlled release.
  - Allow incorporation of both hydrophilic and lipophilic drugs.
  - Potential carriers for synthetic–herbal combinations, enabling dual solubility and synergistic effects [106].

2. Excipients and Penetration Enhancers [107]

Excipients form the backbone of cream formulations, determining spreadability, absorption, and overall therapeutic efficacy.

- **Emulsifiers:** Maintain stability of O/W or W/O systems. Examples: polysorbates, sorbitan esters, cetyl alcohol, stearyl alcohol, glyceryl monostearate.
- **Humectants and Moisturizers:** Prevent drying of the cream and improve skin hydration, which enhances drug penetration. Examples: glycerol, propylene glycol, sorbitol.
- **Thickeners/Gelling Agents:** Provide appropriate viscosity and texture. Examples: carbopol, hydroxypropyl methylcellulose (HPMC), xanthan gum.
- **Oils and Fatty Acids:** Act as both emollients and solubilizers for lipophilic antifungals. Examples: isopropyl myristate, mineral oil, coconut oil, neem oil.
- **Preservatives:** Prevent microbial contamination. Examples: parabens, benzyl alcohol, phenoxyethanol.
- **Antioxidants:** Stabilize both synthetic drugs and herbal oils, preventing oxidation. Examples: butylated hydroxytoluene (BHT), vitamin E (tocopherol).
- **Penetration Enhancers:** Critical for overcoming the barrier of the stratum corneum and ensuring adequate drug delivery to deeper skin layers:
  - **Chemical Enhancers:** Ethanol, dimethyl sulfoxide (DMSO), propylene glycol, oleic acid.
  - **Natural Enhancers:** Terpenes from tea tree, eucalyptus, or clove oil, which disrupt lipid packing in the stratum corneum.
  - **Lipid-based Enhancers:** Phospholipids and surfactants used in nanoemulsions or liposomal creams.

For synthetic–herbal formulations, herbal oils often serve a dual role as active antifungal agents and natural penetration enhancers.

3. Stability Considerations [108]

Ensuring physical, chemical, and microbiological stability is crucial for the long-term effectiveness of antifungal creams.

- **Physical Stability:**
  - Creams must resist phase separation, creaming, or coalescence during storage.
  - Use of proper emulsifiers, stabilizers, and homogenization techniques ensures consistency.
  - Accelerated stability testing (temperature, humidity, and centrifugation) is performed to predict shelf life.
- **Chemical Stability:**
  - Antifungal drugs (e.g., azoles) are prone to degradation under heat, light, or oxidative stress.
  - Herbal oils are highly susceptible to oxidation, requiring antioxidants such as vitamin E or BHT.
  - The pH of the cream base must be optimized (generally pH 4.5–6.5) to prevent drug hydrolysis or loss of activity.
- **Microbiological Stability:**
  - Creams are vulnerable to microbial contamination due to their aqueous content.
  - Broad-spectrum preservatives must be included, and formulations should pass standard preservative efficacy tests (PET).
- **Compatibility of Synthetic-Herbal Combinations:**
  - Synthetic drugs may interact with herbal oil phytoconstituents, potentially affecting drug stability.
  - Preformulation studies, FTIR, DSC, and HPLC analysis are required to confirm drug-excipient compatibility.
- **Packaging Considerations:**
  - Light-sensitive drugs and oils require opaque or aluminum tubes.
  - Air-tight packaging helps prevent oxidation and evaporation of volatile herbal components (e.g., terpenes in tea tree oil).

7. Characterization and Evaluation Parameters

The efficacy and safety of antifungal creams are not solely dependent on the active drug but also on the formulation's physicochemical properties, release behavior, biological activity, and tolerability. Comprehensive characterization ensures quality control, reproducibility, and clinical effectiveness. This section outlines the critical parameters used in evaluating topical antifungal creams [109].

1. Physicochemical Characterization [110]

Physicochemical parameters provide insights into the **stability, uniformity, and patient acceptability** of antifungal cream formulations.

- **Appearance and Homogeneity:**
  - The cream should be smooth, uniform, and free from grittiness or phase separation.
  - Color, odor, and texture are assessed visually.
- **pH Measurement:**
  - The pH should fall within the **physiological skin range (4.5-6.5)** to avoid irritation.
  - Ensures drug stability, especially for **azole antifungals** which are pH-sensitive.
- **Viscosity:**
  - Measured using a **Brookfield viscometer** or rotational rheometer.
  - Optimal viscosity ensures spreadability, residence time, and patient compliance.
  - Both shear-thinning and thixotropic behavior are desirable for topical application.
- **Spreadability:**
  - Determines ease of application and uniform distribution on skin.
  - Typically evaluated by the **slip and drag method** or by measuring the time required for the cream to spread between glass plates under weight.
- **Drug Content Uniformity:**

- Ensures consistent dosing in each application.
- Analyzed using spectrophotometric or chromatographic methods (e.g., HPLC).

- **Globule Size and Distribution (for emulsion-based creams):**
  - Dynamic light scattering (DLS) or microscopy is used.
  - Smaller globule size improves stability and drug penetration.

2. *in Vitro* Drug Release Studies [111]

Drug release from the cream base provides insights into **availability of the active agent at the site of infection**.

- **Diffusion Studies:**
  - Conducted using **Franz diffusion cells** with a synthetic membrane (cellophane, dialysis membrane) or biological membrane (porcine/bovine skin).
  - The release medium is usually phosphate buffer (pH 5.5–7.4), simulating skin conditions.
- **Release Kinetics:**
  - Data fitted to models (zero-order, first-order, Higuchi, Korsmeyer–Peppas) to understand mechanism of release.
  - Controlled or sustained release is desirable for prolonged antifungal activity.
- **Comparative Studies:**
  - Synthetic–herbal combination creams are compared with single-drug formulations to confirm improved release and bioavailability.

3. Antifungal Activity Assays [112]

Evaluation of antifungal activity ensures that the **drug retains potency after formulation** and that synergistic effects (synthetic + herbal) are validated.

- **Agar Diffusion Method (Zone of Inhibition):**
  - The cream is applied on fungal-inoculated agar plates (*Candida albicans, Aspergillus niger, Trichophyton rubrum*).
  - Zone diameter indicates antifungal activity.
- **Broth Dilution/MIC (Minimum Inhibitory Concentration):**
  - Determines the lowest concentration at which fungal growth is inhibited.
  - Useful for quantifying synergistic effects of synthetic–herbal formulations.
- **Time-Kill Assays:**
  - Evaluates fungicidal versus fungistatic action over time.
  - Demonstrates whether combination therapy accelerates fungal clearance.
- **Ex Vivo Skin Models:**
  - Human cadaver skin or animal skin models used to test antifungal efficacy under physiologically relevant conditions.

4. Safety and Irritation Studies [113]

Ensuring safety and tolerability is critical for **long-term use of topical antifungal creams**.

- **Skin Irritation Test:**
  - Performed on animal models (e.g., Wistar rats, rabbits) by applying the cream to shaved skin.
  - Signs of erythema, edema, or irritation are scored according to standardized guidelines (e.g., OECD protocols).
- **Patch Test (Human Volunteers):**
  - Small amount of cream applied to forearm or back for 24–48 hours.
  - Checked for redness, itching, or allergic reaction.
- **Sensitization Studies:**
  - Evaluates allergic potential upon repeated application.
- **Cytotoxicity and Biocompatibility:**
  - In vitro testing on keratinocyte or fibroblast cell lines to ensure safety of both synthetic drug and herbal oil excipients.
- **Photostability and Photosensitivity:**
  - Assessed for creams containing herbal oils (e.g., babchi oil, which has psoralens known for photosensitivity).
  - Prevents adverse phototoxic reactions.

8. Challenges in Developing Synthetic–Herbal Creams

Synthetic–herbal oil-based topical creams offer **synergistic antifungal efficacy** by combining the targeted potency of synthetic drugs with the multi-mechanistic action of herbal oils. However, developing such formulations poses unique challenges. These challenges arise from the **complex nature of herbal constituents, formulation stability, and potential drug-herb interactions**. Addressing these issues is critical to ensure the safety, efficacy, and reproducibility of these advanced topical therapies [114].

1. Stability of Herbal Oils [115]

Herbal oils are inherently **sensitive to environmental factors**, which can compromise the stability and efficacy of the final cream:

- **Oxidative Degradation:**
  - Many essential oils (tea tree, babchi, clove) contain terpenes, furanocoumarins, or phenols that **oxidize rapidly** when exposed to air, light, or heat.
  - Oxidation can reduce antifungal potency and produce **irritant or allergenic by-products**.
- **Volatility of Active Components:**
  - Terpenes and volatile oils may **evaporate during storage or processing**, reducing the effective concentration in the cream.
- **Interaction with Cream Base or Synthetic Drugs:**
  - Certain oils may undergo **hydrolysis or saponification** in the presence of emulsifiers, surfactants, or pH-sensitive synthetic drugs.
  - Lipophilic oils may destabilize O/W emulsions, causing **phase separation**.
- **Mitigation Strategies:**

- Incorporation of **antioxidants** (vitamin E, BHT), opaque packaging, and low-temperature storage.
- Use of **nanoemulsions, liposomes, or encapsulation techniques** to protect labile components.

2. Standardization of Phytoconstituents [116]

Herbal oils are complex mixtures of multiple bioactive compounds, and their **composition can vary widely** depending on origin, harvest season, extraction method, and storage:

- **Batch-to-Batch Variability:**
  - The concentration of active compounds (e.g., bakuchiol in babchi oil, nimbidin in neem oil, terpinen-4-ol in tea tree oil) may fluctuate, leading to **inconsistent antifungal activity**.
- **Lack of Regulatory Guidelines:**
  - Unlike synthetic drugs, herbal oils often **lack stringent pharmacopeial standards**, making quality control challenging.
- **Analytical Challenges:**
  - Identification and quantification of multiple phytoconstituents require sophisticated techniques such as **HPLC, GC-MS, and LC-MS/MS**.
  - Standardization is critical to ensure **reproducibility, efficacy, and safety**.
- **Mitigation Strategies:**
  - Selection of authenticated plant sources and controlled extraction processes.
  - Development of **marker-based standardization** (e.g., psoralen content in babchi oil, azadirachtin in neem oil).
  - Quality control protocols to monitor **active component concentration and purity**.

3. Risk of Interactions [117]

Combining synthetic antifungals with herbal oils introduces the possibility of **chemical or pharmacological interactions**, which may affect **stability, efficacy, or safety**:

- **Chemical Interactions:**
  - Reactive phytoconstituents (phenols, aldehydes, terpenes) can react with synthetic drugs, leading to **degradation or loss of potency**.
  - Emulsion stability may be compromised if oils interact with surfactants or emulsifiers.
- **Pharmacodynamic Interactions:**
  - While many interactions are synergistic, antagonistic effects are possible.
  - For example, some oils may alter the pH or permeability of the cream, affecting the **activity of azoles or allylamines**.
- **Toxicological Risks:**
  - Certain phytoconstituents may enhance **skin irritation, allergenicity, or photosensitivity** (e.g., psoralens in babchi oil).
  - Safety evaluation is essential to avoid **adverse dermatological reactions**.
- **Mitigation Strategies:**
  - Conduct **preformulation compatibility studies** using FTIR, DSC, or stability testing.
  - Optimize concentrations of both synthetic and herbal components to minimize irritation or antagonism.
  - Employ **encapsulation or controlled-release systems** to separate incompatible components within the cream matrix.

9. Future Perspectives

The treatment of superficial fungal infections is evolving beyond conventional topical creams, driven by the need for enhanced efficacy, reduced resistance, improved patient compliance, and safer formulations. Synthetic–herbal combination creams have shown promising results, but their full potential can be realized through advanced drug delivery systems, personalized therapy approaches, and clear regulatory frameworks. Conventional cream bases, while effective, have limitations such as poor drug penetration, instability of herbal oils, and limited controlled release. Advanced nano- and micro-carrier systems can address these challenges and optimize therapeutic outcomes. Nanoemulsions, which are oil-in-water or water-in-oil systems with droplet sizes below 200 nm, enhance the solubility and bioavailability of lipophilic antifungals and herbal oils, improve skin penetration by disrupting stratum corneum lipid packing, and offer controlled release with prolonged antifungal activity. For instance, terbinafine–tea tree oil nanoemulsions have been reported to accelerate dermatophyte eradication. Cubosomes, nanostructured lipid cubic phases capable of encapsulating both hydrophilic and lipophilic actives, provide high drug loading capacity, sustained release properties, and protection of sensitive herbal oils from oxidation and degradation; an example includes clotrimazole–neem oil-loaded cubosomal creams demonstrating enhanced permeation and synergistic antifungal effects. Liposomes, phospholipid vesicles encapsulating drugs and oils, facilitate targeted delivery to skin layers, reduce systemic absorption, improve stability of volatile herbal oils, and minimize skin irritation, allowing controlled co-delivery of synthetic drugs and herbal phytoconstituents. Other advanced systems, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), hydrogels, and bioadhesive films, further enhance stability, penetration, and localized drug retention. These novel systems not only improve antifungal efficacy but also enable lower dosing, reducing side effects and overall treatment costs [118].

The concept of personalized or precision antifungal therapy is gaining traction, particularly as fungal infections increasingly display variable susceptibility patterns and patient-specific responses. Genetic and microbiome profiling can reveal individual differences in skin microbiota, immune response, and enzymatic activity that influence treatment outcomes, enabling cream formulations to be tailored to specific fungal strains and patient skin characteristics. Customized synthetic–herbal combinations allow selection of specific herbal oils or concentrations to complement synthetic drugs according to fungal susceptibility and patient tolerance, promoting synergistic therapy while minimizing adverse effects. Smart formulations are being developed to release the drug in response to local pH changes, fungal enzymes, or moisture levels, optimizing drug availability at the site of infection, reducing wastage, and improving patient compliance. Personalized therapy has the potential to reduce recurrence rates, shorten treatment duration, curb the emergence of resistant strains, and provide patient-friendly solutions [119].

The integration of synthetic drugs with herbal oils presents regulatory challenges due to the complexity of active components. Quality control and standardization are critical, requiring that herbal oils be standardized for active constituents with batch-to-batch consistency and that synthetic drug meet pharmacopeial

standards. Comprehensive stability, purity, and safety testing is essential for regulatory approval. Safety and toxicity evaluation for combination products must include preclinical studies assessing irritation, sensitization, and phototoxicity, taking into account both synthetic drugs and herbal phytoconstituents. Approval pathways vary across regions; in India, guidelines from AYUSH and CDSCO govern herbal and combination products, while in the US and EU, combination products may require evaluation of both botanical drugs and conventional drugs. Clear documentation of efficacy, stability, and safety is necessary for regulatory approval. Accurate labeling of herbal content, concentration, and therapeutic claims is crucial to meet regulatory standards and avoid misleading consumers. Intellectual property considerations, including patenting of synthetic–herbal combinations and novel delivery systems, can promote innovation but require demonstration of novelty, utility, and stability [120].

2. CONSLUSION

Synthetic–herbal oil-based topical creams represent a promising and innovative approach for the management of superficial fungal infections. By combining the targeted potency of synthetic antifungal agents with the multi-targeted, bioactive properties of herbal oils, these formulations offer enhanced efficacy, faster symptom relief, and reduced risk of resistance. Advances in formulation strategies, including optimized cream bases, penetration enhancers, and stability considerations, are critical to maximize therapeutic outcomes. Comprehensive characterization and evaluation covering physicochemical properties, in vitro drug release, antifungal activity, and safety assessments ensure quality, reproducibility, and patient acceptability. Despite their potential, the development of these hybrid formulations poses challenges such as herbal oil instability, variability in phytoconstituents, and possible drug–herb interactions, which must be carefully addressed. Future perspectives, including novel delivery systems (nanoemulsions, cubosomes, liposomes), personalized antifungal therapy, and adherence to regulatory frameworks, promise to overcome current limitations and optimize treatment outcomes. Overall, synthetic–herbal combination creams hold significant potential as safe, effective, and patient-friendly alternatives to conventional antifungal therapies, marking a step forward in integrated and modern topical antifungal treatment strategies.

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