RESEARCH PAPER

Herbal Microemulsion-Based Drug Delivery Systems for Enhanced Antifungal Therapy: A Comprehensive Review

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ABSTRACT

Fungal infections are a problem for people all around the world especially for those who have weak immune systems. This is because fungal infections can make people very sick and even cause death. Doctors usually treat infections with medicines like azoles, allylamines, echinocandins, polyenes and antimetabolites. Fungal infections are a deal and we need to find better ways to treat them. The problem with these medicines is that they can have side effects do not work well in the body and people have to take them for a long time. Also, some fungi are becoming resistant, to these medicines. This means we really need to find better ways to treat fungal infections. Herbal antifungal agents from plants are getting more attention because they have many bioactive phytochemicals like flavonoids and terpenoids. These phytochemicals, which also include phenolics and alkaloids are good at fighting fungus. They work in ways, such, as damaging the fungus cell membrane stopping the fungus from making ergosterol causing oxidative stress and preventing the fungus from forming a biofilm. Herbal antifungal agents have a lot of potential to help people. It is hard to use them as medicine because they do not dissolve well in water they are not very stable and they have a hard time getting through the skin.

Microemulsion-based drug delivery systems are a way to deal with these problems. These tiny systems are stable. They help herbal bioactives to be absorbed and to last longer in the body. This makes the treatment work better. The drug is released in a controlled way. This review talks about the types of fungal infections the problems with the treatments that are available now and the new developments in herbal microemulsion formulations. Herbal microemulsion formulations have the potential to be more effective treatments, for fungal infections and they can be used in clinics.

Keywords: Fungal infections; Immunocompromised; Antifungal Therapies; Bioactive Phytochemicals; Ergosterol Biosynthesis; Microemulsion; Herbal bioactives.

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1. INTRODUCTION

Fungal infections are a problem for people everywhere in the world. Two thirds of the people in the world get fungal infections. A lot of people die from diseases every year. The quantity of deaths caused by illnesses is really high. It is around 3.75 million people per year. This is a lot more than it used to be. Before it was around 1.5 to 2 million people per year. Most of these deaths 68 percent are because of infections. This is around 2.5 million people. These numbers are high because a lot of people do not know about infections. Also, some people are more susceptible to infections than others. People are included in this who're sick or have weak immune systems. Fungal infections can be mild or severe [1]. They can affect the skin or the inside of the body. Some fungi, like *Candida* are normally found on our bodies. They can cause problems for people who're sick. For example, people with HIV or cancer can get very sick from *Candida.* People who take medicine that weakens their system can also get sick. Fungi like *Candida*, *Aspergillus* and *Fusarium* can cause problems for people who're already sick. They can get infections in the hospital, which can be very bad. This is especially true, for people who have health problems. Fungal infections are a deal and we need to know more about them to stay safe. Fungal infections are a problem in areas. They cause diseases like *Blastomycosis*, *Coccidiodomycosis*, *Histoplasmosis*, *Talaromycosis*, *Paracoccidiodomycosis* and *Sporotrichosis* [2]. Fungal skin infections are common because fungi love to eat keratin. Keratin is a protein found in our nails, skin, and hair. Skin infections caused by fungi can cause symptoms. You may get a scaly, itchy and dry rash. Sometimes the rash can be really bad. Symptoms of skin

infections can look different on people. For example, one person gets a rash while another person gets a small itchy spot. Doctors usually prescribe medicines that you put directly on your skin to get rid of infections. These medicines come in forms, like lotions, sprays, gels and creams. Doctors like to use these medicines because they help kill the fungi that cause the infection. Sometimes doctors also give you medicines that you take by mouth. These medicines are called fluconazole, itraconazole and micafungin. Fungal infections are treated with these medicines because they help kill the fungi that cause infections [3]. Fungal infections remain a major therapeutic challenge despite the availability of several conventional antifungal agents. Triazole derivatives such as Luliconazole, Ketoconazole, Sertaconazole, and Eberconazole are commonly prescribed for the treatment of fungal infections; however, their use is often associated with adverse effects including itching, skin irritation, rashes, and hypersensitivity reactions. In addition, prolonged use of these synthetic antifungal agents may lead to reduced patient compliance and the development of drug resistance. Therefore, there is an increasing need to develop safer and more effective alternatives for antifungal therapy. In this context, plant-based medicines have attracted considerable attention due to their natural origin, therapeutic potential, and comparatively better safety profile. Phytochemical studies have demonstrated that medicinal plants contain a wide range of bioactive compounds with significant antifungal activity, suggesting their potential as promising alternatives to conventional synthetic antifungal agents [4]. Microemulsion systems have also emerged as promising carriers for herbal antifungal agents due to their thermodynamic stability, improved solubilization capacity, enhanced skin permeation, and better bioavailability. The nanosized droplet structure of microemulsions facilitates efficient delivery of phytoconstituents at the site of infection, thereby improving antifungal efficacy and therapeutic outcomes [5].

2. CLASSIFICATION OF FUNGAL INFECTIONS

Fungal infections (mycoses) are categorized according to the location and extent of tissue involvement, as well as the method of transmission and the organism's pathogenic potential, as shown in Figure 1.

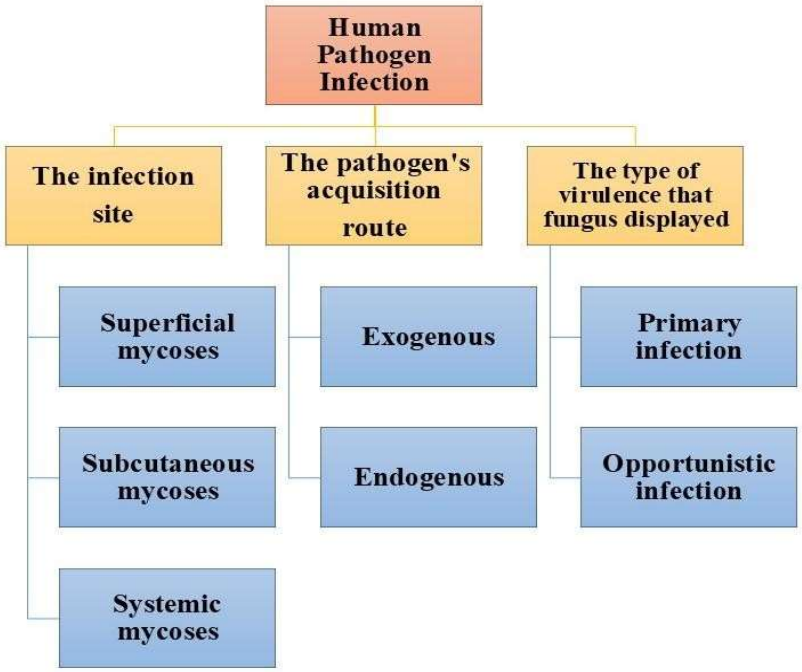


Figure: -1 Classification of fungal infection

Mycoses are fungal diseases that affect humans as well as animals, and they are categorized according to the depth of tissue involvement at the initial stage of infection. The clinical classification is further based on parameters such as anatomical site, route of acquisition, and pathogenic potential of the organism [6]

2.1. Classification Based On The Infection Site

Mycoses are basically kinds of infections. They can be on the surface of the skin. They can be in the skin or even deeper. Doctors group Mycoses, into four types: superficial Mycoses, cutaneous Mycoses, subcutaneous Mycoses or systemic Mycoses. The type of Mycoses depends on how bad the infection's how the body reacts to the bad guy that is causing the infection, which is called a pathogen [7]. The

categorization by site, together with their main characteristics and responsible organisms, is outlined in Table 1.

Table: -1 Classification Based on the infection site

Type of Mycoses	Sites Involved	Key Features	Example / Causative Organism	Reference
I. **Superficial Mycoses**	Outer skin and hair	Affects outer skin; causes discolored spots; common in humid areas.	*Malassezia furfur* (Tinea versicolor)	[8]
II. **Cutaneous Mycoses**	Epidermis, hair, nails	Infect keratinized tissues; cause ringshaped itchy lesions.	*Trichophyton*, *Microsporum*, *Epidermophyton*	[9]
III. **Subcutaneous Mycoses**	Dermis, subcutaneous tissue, muscle	Enters via trauma; chronic nodules; may need surgery.	*Sporothrix schenckii*, *Cladosporium* spp.	[10]

I. Superficial mycoses

The skin and hair can get a kind of infection that only affects the outer layers. This is called a mycoses. For example, there is *Tinea versicolor*. It is an infection that a lot of young people get. Tinea versicolor usually shows up on the upper portions of the arms and legs, as well as the chest and back. Tinea versicolor is caused by a fungus that lives on the skin of some adults. Typically, it doesn't show up on the face. This fungus can make spots on the skin they are either reddish-brown or lighter color. *Tinea versicolor* comes in two forms one of them makes spots that you can see. Some things that can make the fungus more noticeable are when it is really humid and when there are problems, with the system or hormones. Even though *Tinea versicolor* is very common people who have it are usually healthy [8].

II. Cutaneous mycoses

Skin infections like mycoses go deeper into the skin. They can also affect the hair and nails. These infections only happen in the layers of the nails, hair, and skin. Dermatophytes are the organisms that cause these illnesses. The illnesses that come from these infections are frequently referred to as *tinea, dermatophytosis,* or *ringworm*. Cutaneous mycoses are a type of infection that can cause a lot of problems for the nails, hair, and skin. The dermatophytes responsible for mycoses are very good, at infecting the skin, hair and nails [9].

III. Subcutaneous mycoses

Skin infections like mycoses affect the skin and the tissues underneath. Subcutaneous mycoses can get into the dermis and the subcutaneous tissues. Even, into the muscle and fascia. These subcutaneous mycoses infections are term and usually start when something pierces the skin and lets the fungi in. Subcutaneous mycoses infections are hard to get rid of. Sometimes doctors have to do surgery to fix the problem like removing the bad tissue which is called debridement [10].

2.2. Classification Based On The Pathogen's Acquisition Route

Depending on how they enter the host, infecting fungus can be categorized as either endogenous or exogenous.

i Exogenous infections

These happen when fungus get inside the host from outside. Typical entry points consist of:

Fungal spore inhalation is airborne.

- **Cutaneous:** Direct skin touch
- **Percutaneous:** Via skin or mucous membrane fissures.

ii Endogenous infections

These problems come from fungi that are normally found in the hosts body or because of an infection that starts up again [11].

Table 2 provides more information about the detailed classification depending on the acquisition path.

Table: -2 Classification Based on Route of Acquisition

Type of Infection	Source / Route of Entry	Examples	Key Features (Short)
I. **Exogenous Infections**	Acquired from external environment		Infections originate outside the body and enter through different routes.
a) **Airborne**	Inhalation of fungal spores	*Aspergillus*, *Histoplasma*	Enters via respiratory tract.
b) **Cutaneous**	Direct contact with infected material or skin	*Dermatophytes* (Tinea)	Affects skin, hair, nails.
c) **Percutaneous**	Through wounds or skin breaches	*Sporothrix*	Enters via trauma; subcutaneous

		schenckii	infection.
II. **Endogenous Infections**	From normal flora or reactivation of latent infection	*Candida albicans*	Occurs when host immunity is compromised.

2.3. Classification Based On Virulence

Normal hosts are susceptible to infection by primary pathogens. People with weakened host defense systems are susceptible to illness from opportunistic infections.

i. Primary pathogen-induced systemic mycoses:

The lungs are the principal site of mycoses caused by primary infections, which can spread to several organ systems. Systemic mycoses are caused by organisms that are virulent by nature. Systemic mycoses are typically caused by dimorphic main infections [12].

ii. Systemic mycoses brought on by opportunistic infections

Patients with immune deficits who would not otherwise be infected can develop mycoses caused by opportunistic microorganisms. AIDS, antibiotic-induced change of natural flora, immunosuppressive medication, and metastatic cancer are examples of situations that are not compromised.

Aspergillosis, *cryptococcosis*, and *candidiasis* are a few instances of opportunistic mycoses [13].

iii. Opportunistic Mycosal disease Candidiasis

The most prevalent *Candida albicans* and other *Candida* species cause candidiasis, an opportunistic fungal infection. The most frequent cause of candidiasis is *Candida albicans*. There are two types of candidiasis: superficial and profound. The mouth, throat, esophagus, intestines, bladder, and vagina's mucosal and epithelial surfaces can all be affected by superficial candidiasis. The two primary entry sites for visceral or deep candidiasis are the digestive system and intravascular catheters. The kidneys, liver, spleen, brain, eyes, heart, and other tissues are primarily affected by deep or visceral candidiasis. Prolonged regimens of wide vascular catheters, corticosteroids, cytotoxic chemotherapy, and spectrum antibiotics are the primary risk factors for highly invasive candidiasis.[14].

3. PATHOPHYSIOLOGY OF FUNGAL INFECTION

The way fungal infections work is that they stick to grow on and get into the tissues of the body, which can damage the tissues because the fungi make things like enzymes and toxins. When this happens, the body tries to fight the infection. People, with weak immune systems might get very sick because the infection can spread. The main things that happen when someone gets an infection are shown in Figure 2 [15-17]. Fungal infection is a problem and fungal infection can cause a lot of damage. The body tries to stop infection from spreading.

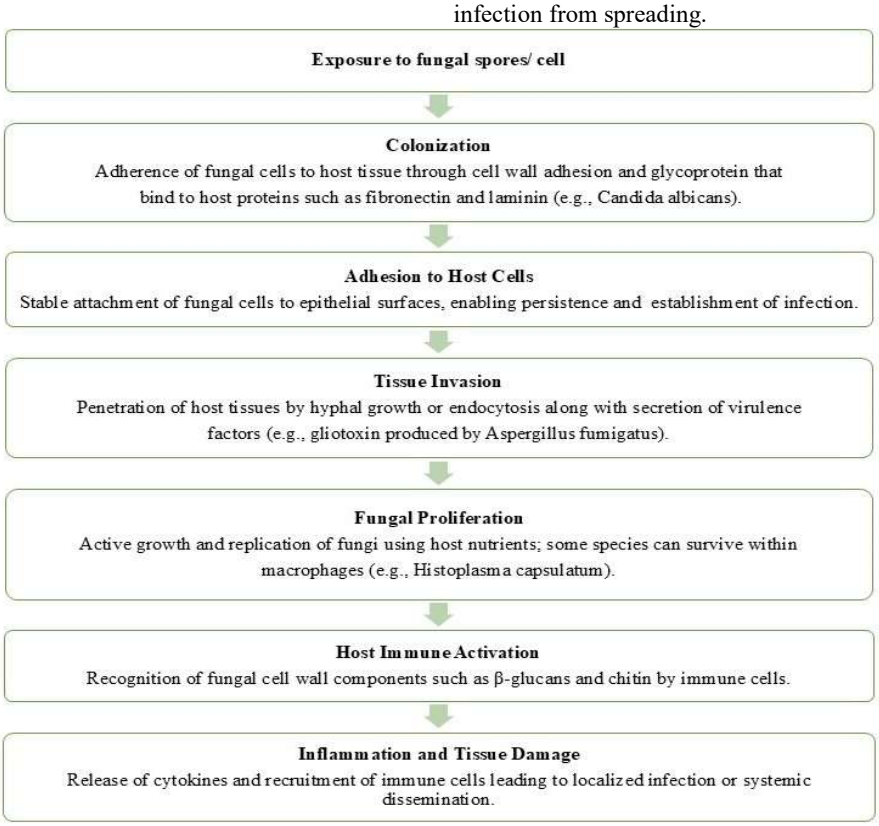


Figure: -2 Pathophysiology of Fungal Infection

3.1 Skin Barrier Role

The skin acts as a critical physical barrier that prevents fungal entry and protects the body from pathogenic invasion. The outermost layer, the stratum corneum, consists of corneocytes and lipids that maintain hydration and restrict microbial penetration. Beneath this, the stratum granulosum contains tightly packed cells that further strengthen barrier integrity, while the stratum basale is responsible for continuous regeneration of epidermal cells, ensuring maintenance of skin structure and function [18].

In addition to its structural role, the skin possesses an active immune defense system. Epithelial cells can recognize fungal pathogens and initiate immune responses by releasing signaling molecules and antimicrobial proteins that inhibit fungal growth [19]. Furthermore, resident immune cells, including Langerhans cells, macrophages, and dendritic cells, play a vital role in pathogen recognition and activation of host defense mechanisms. These cells work in coordination with skin cells to control fungal proliferation and maintain cutaneous health [20].

The skin barrier and its immune cells help keep us safe from things. They keep us safe from things like fungi and other stuff that can hurt us. When the skin barrier gets hurt because it is too wet or we get an injury fungi can stick to the skin. Cause problems. This is not good for us. The skin barrier is like a wall around us that keeps things out. When this wall is broken fungi can get inside cause trouble [21]. This can lead to infections. That is very bad. Fungi that get inside the skin make things that break down the skin. This makes the skin get red and swollen. It can be very painful. So we need to keep the skin barrier strong. This will help keep fungi from getting and causing infections. We do not want that to happen. The skin barrier and its immune cells are, like our protectors. They defend us against fungi and other bad things that can hurt us. We must take care of our skin barrier so we can stay safe from fungi infections and be healthy [22].

4.CONVENTIONAL ANTIFUNGAL THERAPY

Major classes of antifungals include allylamines such as terbinafine, azoles, echinocandins, antimetabolites such as flucytosine, polyenes.

4.1 Drugs

Allylamines

Allylamines are a type of medicine that helps fight fungus. They are used to treat infections that affect the skin, hair and nails. Allylamines come in creams and pills. They work well and most people can take them without any problems [23]. Allylamines like terbinafine and naftifine are very good at fighting kinds of fungus. Doctors usually give people these medicines for things like athletes foot, ringworm and fungus in the nails. These medicines are good at stopping squalene epoxidase. Squalene epoxidase is an enzyme that helps to make ergosterol. The fungus needs ergosterol to survive. When the medicine stops squalene epoxidase the fungus cannot make ergosterol. This is bad for the fungus because it cannot work properly without ergosterol. The fungus will die. Allylamines are good, at killing fungus because they stop the fungus from making what it needs. Allylamines target the fungus [24].

Azoles

Azoles are widely used antifungal agents classified into imidazoles (e.g., miconazole, ketoconazole) and triazoles (e.g., fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole). Imidazoles are mainly used for topical or limited systemic infections, while triazoles are commonly prescribed for systemic fungal infections. Azoles exert their antifungal activity by inhibiting ergosterol synthesis through blockade of a key fungal enzyme, leading to disruption of cell membrane integrity and fungal cell death. However, their use may be associated with drug interactions and hepatotoxicity [25].

Echinocandins

Caspofungin, micafungin, and anidulafungin are members of the significant class of antifungal drugs known as echinocandins, which were identified in the 2000s. They are lipophilic side chains in cyclic hexapeptides that make up non-ribosomal lipopeptides. They are lyophilized powders that are water soluble and administered intravenously because of limited absorption in the digestive system. Echinocandins are generally well tolerated and have fewer medication interactions than azoles [26]. They have fungistatic properties against *Aspergillus* and fungicidal properties against *Candida* species. By binding to the Fks1p subunit, they inhibit β(1,3)-D-glucan synthase, preventing the production of β-(1,3)-D-glucan, a crucial part of the fungal cell wall. Although their effectiveness against some fungal species is restricted, this causes cell wall instability and fungal cell death [27].

Flucytosine

Flucytosine, also known as 5-fluorocytosine, or 5-FC, is a synthetic pyrimidine analogue introduced as an antifungal medication in 1968. It is effective against fungi such as *Candida tropicalis*, *Candida lusitaniae, Candida albicans, Candida glabrata, Candida parapsilosis,* and *Cryptococcus neoformans* are among the fungus that flucytosine effectively combats. It can be taken orally or intravenously, and it is transformed into 5-fluorouracil (5-FU) when it reaches fungal cells via cytosine permease. This metabolite suppresses the growth of fungal cells by interfering with RNA by preventing the synthesis of proteins and DNA by preventing the synthesis of thymidylate synthetase [28].

Polyenes

Since their discovery in the 1950s, polyenes—such as amphotericin B, nystatin, and natamycin—remain crucial antifungal medications because of their wide-spectrum action and low rates of resistance. Many different types of fungi, including *Histoplasma, Aspergillus, Fusarium, Cryptococcus, Candida, Blastomyces, Coccidioides, Mucor,* and *Sporothrix species*, can be effectively treated with amphotericin B. By attaching to ergosterol in the fungal cell

membrane, polyenes cause hole development, intracellular content leakage, and ultimately fungal cell death [29].

4.2. Limitations

The most prevalent adverse effect of **allylamines**, such terbinafine, on the central nervous system is a headache. Rashes, diarrhea, dyspepsia, and upper respiratory inflammation or infection are further signs of adverse events [30].

Although **azole** antifungals are usually well tolerated, they frequently result in Nausea, vomiting, diarrhea, and stomach discomfort are examples of gastrointestinal adverse effects. One significant restriction is hepatotoxicity, which includes increased liver enzymes, hepatitis, and infrequently, liver failure. Drug efficacy may be decreased by resistance that arises from mutations in target enzymes and efflux pumps. Azoles also inhibit CYP450 enzymes, which increases the risk of toxicity and causes serious drug-drug interactions [31].

Hepatotoxicity, hypotension, infusion-related responses, phlebitis, gastrointestinal problems, electrolyte imbalances, and anemia are all possible side effects of **echinocandins**. Because they don't have an oral formulation and must be administered intravenously, their long-term use is limited by their susceptibility to resistance and chemical deterioration [32].

Flucytosine can cause side effects. Some of the serious ones affect the blood, like agranulocytosis aplastic anemia and pancytopenia. People may also experience stomach problems, such as nausea and abdominal pain. Liver damage and kidney damage are possible. Flucytosine can also cause confusion, headache and hallucinations. Some individuals may have nerve damage leading to neuropathy. Additionally skin reactions like rash and itching can occur. These side effects show that Flucytosine and its effects, on the body need monitoring. Flucytosine side effects can be severe so patients taking Flucytosine should be aware of them [33].

Significant toxicity limits the use of **polyenes**, especially amphotericin B and related formulations. Nephrotoxicity, which includes renal failure and high serum creatinine levels, is the main drawback. They are also linked to electrolyte imbalances (hypokalemia, hypomagnesemia), anemia, and infusion-related responses as fever, chills, rigors, hypotension, and headache [34].

4.3. Resistance

Single-nucleotide variants (SNVs) in the SQLE gene, encoding squalene epoxidase, are the primary cause of **allylamine** resistance to terbinafine resistance. Dermatophytes like Trichophyton rubrum, Trichophyton mentagrophytes, and Trichophyton indotineae often have common mutations like Phe397Leu and Leu393Ser, which are linked to high treatment resistance [35]. Although there have been reports of another mutation, Ala448Thr, its precise function in resistance is still unknown. Additionally, mutations in the *ERG11* gene may contribute to reduced susceptibility to azole antifungals. [36].

Genetic alterations are the primary cause of **azole** resistance in fungus. Mutations in the ERG11 gene result in azole resistance by reducing the azole's ability to bind to the enzyme's active site [37]. Two genes, cyp51A and cyp51B, encode the Cyp51 isoenzymes in A. fumigatus. Mutations in cyp51A result in resistance to triazole, while mutations in cyp51A give resistance to voriconazole. Another resistance mechanism is increased efflux, which is mediated by the major facilitator superfamily transporters (MSF transporters) and ATPbinding cassette transporters (ABC) [38, 39].

Echinocandins resistance is something that happens mainly because of changes in the one three glucan synthase enzymes called FKS1. This is found in things like *Candida* and *Cryptococcus* and *Aspergillus*. There is also another one called FKS2 that is found in C. Glabrata. When we look at Candida we see that changes in the FKS1 enzyme can make it resistant to echinocandins. This is especially true for things like *C. Albicans and C. Tropicalis, P. Kudriavzevii* and *C. Glabrata* [40]. These changes in the FKS1 enzyme are like a switch that turns on the resistance. They are called gain of function mutations. They happen in certain areas of the enzyme [41].

The rapid development of **flucytosine** (5-FC) resistance restricts its application in therapeutic treatment. This resistance typically results from increased pyrimidine synthesis, or enzyme mutations or deletions that affect its transport and metabolism. Because of this, 5-FC is usually advised in conjunction with other antifungals and is rarely used as a monotherapy. It is used in conjunction with AmB or voriconazole to treat invasive *Candida* infections, and it is commonly used in conjunction with AmB to treat cryptococcal meningitis [42].

Polyenes resistance to (AmB) is rare and associated changes in the route that produces ergosterol, which causes the buildup of other sterols by removing ergosterol from the membrane. However, resistance frequently leads to trade-offs in fitness, such as heightened susceptibility to neutrophil-mediated death, heightened susceptibility to fever and stress [43].

Table: -3 Major Classes of Antifungal Therapies: Molecular Targets, Mechanisms, Limitations, and Resistance Mechanisms

Antifungal Class	Main Mechanism of Action	Specific Molecular Target	Major Resistance Mechanisms	Activity vs. Key Pathogens	Reference
Allylamines (e.g., Terbinafine)	Inhibits ergosterol synthesis causing accumulation of toxic squalene	Squalene epoxidase (Erg1/SQLE)	Mutations or overexpression of SQLE/ERG1 gene; amino-acid substitutions such as Phe397Leu and Leu393Ser	Fungicidal against dermatophytes such as *Trichophyton rubrum*	[23]
Azoles (e.g., Fluconazole, Itraconazole, Voriconazole, Posaconazole)	Inhibits ergosterol synthesis leading to toxic sterol accumulation	Lanosterol 14α-demethylase (Erg11/Cyp51A)	ERG11/CYP51 mutations, overexpression of target enzyme, increased efflux via ABC and MFS transporters, chromosomal duplications	Fungistatic against yeasts such as *Candida albicans* and active against *Aspergillus fumigatus* [26]	[26]
Echinocandins (e.g., Caspofungin, Micafungin, Anidulafungin)	Prevents the formation of β-(1,3)-D-glucan, Which damages cell walls.	Fks1/Fks2 β-(1,3)-Dglucan synthase	Hotspot mutations in FKS1 or FKS2 genes, particularly in *Candida glabrata*	Fungistatic against *Aspergillus* species; fungicidal against *Candida species* [33]	[33]
Flucytosine	Converted intracellularly to 5-fluorouracil, inhibiting thymidylate synthase and RNA synthesis	Synthesis of DNA and RNA	Mutations in FCY1, FCY2, or FUR1, reduced drug uptake, altered pyrimidine metabolism	Fungistatic against *Candida spp.* and *Cryptococcus neoformans* [37]	[37]
Polyenes (e.g., Amphotericin B, Nystatin)	Binds ergosterol causing pore formation and membrane leakage	Ergosterol in fungal membrane	Reduced ergosterol content due to ERG2, ERG3, ERG6, ERG11 mutations, altered membrane sterol composition (rare)	Broad-spectrum fungicidal activity against *Candida, Aspergillus,* and *Cryptococcus* [42]	[42]

5. RATIONALE FOR EXPLORING HERBAL ANTIFUNGAL AGENTS

Azoles, allylamines, echinocandins, griseofulvin, and flucytosine are the main categories of antifungal medications used in clinical settings to treat fungal infections. Despite the fact that these medications have made it easier to treat fungal illnesses, their usage is frequently restricted due to toxicity, extensive treatment times, and the development of drug resistance [44]. Particularly in pathogenic fungi like *Candida albicans* and the multidrug-resistant species Candida auris, resistance to azole antifungals like fluconazole has becoming more prevalent. These difficulties emphasize the necessity of creating novel antifungal medications. Given that phytochemicals derived from plants have demonstrated encouraging antibacterial and antifungal properties and have been utilized in traditional medicine for ages, medicinal plants have drawn interest as possible sources of antifungal agents [45].

6. HERBAL ANTIFUNGAL AGENTS

Herbal antifungal agents are organic compounds made from therapeutic herbs that have the capacity to stop the growth of or eradicate harmful fungi. Flavonoids, terpenoids, alkaloids, and phenolic compounds are instances of bioactive phytochemicals with antifungal properties that are present in these medications properties via a variety of mechanisms. Due to their possible efficacy, lower toxicity, and decreased risk of resistance when compared to standard antifungal medications, herbal antifungal medicines are being extensively researched as supplementary or alternative therapy for fungal infections [46].

6.1. Mechanism Of Action

• Disruption of Fungal Cell Wall and Membrane

Numerous plant-based substances, such as phenolics, terpenoids and essential oils affect the membrane and fungal cell wall. These substances weaken the cell wall by disrupting its structure, which includes things like chitin and glucans. The plant substances also upset the lipid bilayer of the membrane. This damage causes the fungal cell to lose its components and ultimately leads to cell death. The result is that the fungal cells get damaged. The plant-based substances keep affecting the cell wall and membrane. [47].

• Inhibition of Ergosterol Biosynthesis

The manufacture of ergosterol, a crucial sterol that keeps fungal cell membranes stable and functional, is hampered by some phytochemicals. Fungal growth and survival are eventually hampered by the disruption of membrane permeability and structure caused by a decrease in ergosterol concentration [48].

• Induction of Oxidative Stress

It is possible to produce reactive oxygen species (ROS) inside fungal cells by herbal antifungal medicines. Cellular components such lipids, proteins, and nucleic acids are oxidatively damaged by excessive ROS buildup, which results in cellular malfunction and fungal cell death [49].

• Inhibition of Enzymatic and Metabolic Processes

Some substances originating from plants disrupt metabolic pathways and protein production, as well as block important fungal enzymes. Energy production and vital metabolic processes necessary for fungal growth and replication are impacted by this disruption [50].

• Inhibition of Fungal Virulence and Biofilm Formation

Certain herbal chemicals inhibit the development of biofilms, hyphal production, adhesion, and other aspects of fungal pathogenicity. Herbal antifungal drugs decrease fungal colonization, slow the spread of illness, and improve antifungal efficacy by blocking these processes [51].

Figure 3 shows a schematic summary of the mechanism of action.

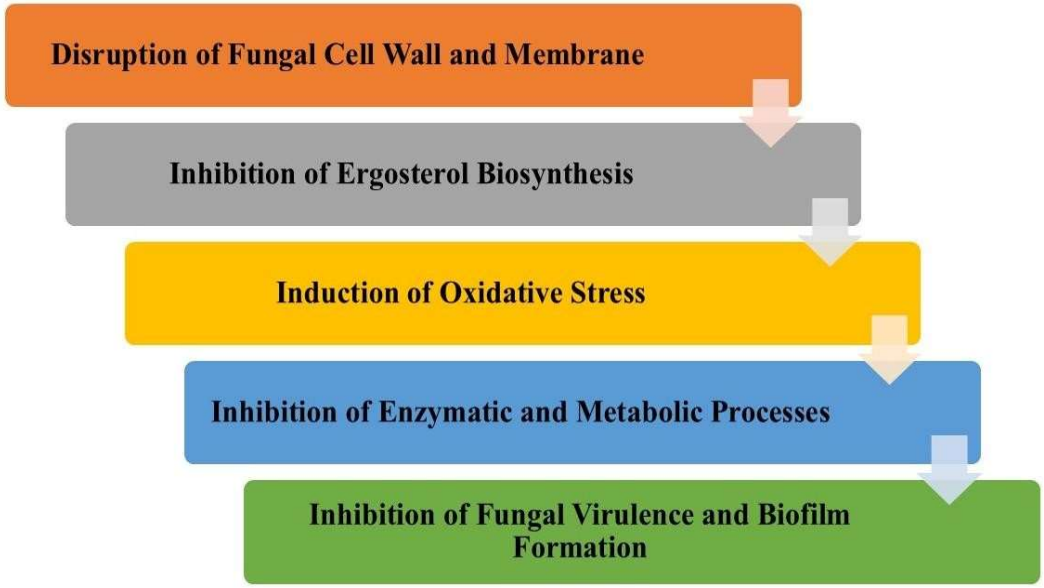


Figure: -3 Mechanism of Action

6.2. Example Of Common Herbs With Antifungal Activity: - Numerous medicinal herbs and plant-based formulations have shown considerable antifungal activity against a variety of pathogenic fungi due to their bioactive phytochemicals. Here are some representative examples-

***Curcuma aromatica* (Wild turmeric):** *Curcuma aromatica*, also known as Wild turmeric has some properties. The main reason *Curcuma aromatica* can fight

off fungus is because of the things it contains like curcuminoids and flavonoids and phenolic compounds. These things are good at messing up fungus cell membranes. Stopping them from working. *Curcuma aromatica* can stop fungus like *Candida albicans* and *Aspergillus flavus* from growing [52].

***Aloe vera* (Aloe)**
Aloe vera is also good at fighting off fungus. Aloe vera contains compounds and anthraquinones and polysaccharides that stop fungus cells from working and growing. These things, in Aloe vera help our bodies fight infections. That makes Aloe vera good at fighting *Candida* species and other fungus [53].

***Azadirachta indica* (Neem)**
Azadirachta indica has a lot of potential to fight off fungus. This is because it has things like azadirachtin, nimbin and nimbolide in it. These things from plants really mess with the walls of cells change how easy it is for things to get in and out of the cell and stop the spores from growing. This means that *Azadirachta indica* is really good at stopping *Candida albicans* and other bad fungi from growing [54].

***Curcuma longa* (Turmeric)**
Curcumin is a part of *Curcuma longa* and it is really good at fighting off fungus too. It does this by changing how easy it is for things to get in and, out of the cell stopping the fungus from making ergosterol and making things that hurt the cells of the fungus. This hurts the fungus like *Candida albicans*. Stops it from working properly [55].

Origanum vulgare* (Oregano*)
The oil from *Origanum vulgare* is really good at fighting fungus. This is because it has a lot of carvacrol and thymol in it. These things are very bad for fungus. They mess up the fungus cells. Cause all the insides to leak out. They also stop the cells from working. This is especially bad for *Candida albicans* [56].

***Syzygium aromaticum* (Clove)**
The oil from *Syzygium aromaticum* is also very good at fighting fungus. This is because it has a lot of eugenol in it. The eugenol damages the fungus cells. Stops them from working. It also stops the proteins in the cells from doing their job. This causes the cells to die. *Candida albicans* is one of the fungi that this oil's very good at killing [57].

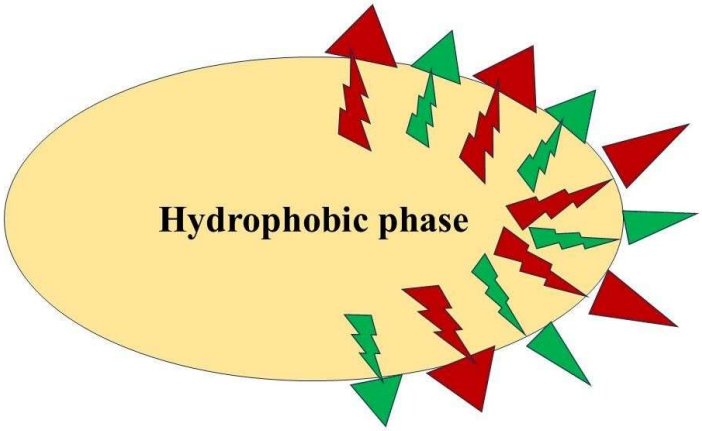
***Lawsonia inermis* (Henna)**
Lawsonia inermis has some ingredients that help it fight fungus. These ingredients are lawsone, flavonoids and tannins. They stop the fungus from building cells. They also stop the proteins in the cells from working. This means that the fungus cannot grow. It is especially bad, for *Candida albicans* and *Aspergillus niger*. [58]

***Cymbopogon citratus* (Lemongrass)**
The antifungal effect of *Cymbopogon citratus* comes from other things called terpenoids. These things hurt the membranes of cells. They also stop the spores from growing. Make it hard for the fungi to breathe. This is especially true for *Candida albicans*.[59]

***Ocimum sanctum* (Tulsi)**
The antifungal activity of sanctum is due to eugenol ursolic acid and some other compounds that have a lot of phenol in them. These compounds mess up the membranes of the cells. Stop the fungi from growing. They do this by interfering with the way the cells make things they need. This happens with *Candida albicans*.[60]
Herbal antifungal agents are pretty good, at what they do. They have some problems. They do not dissolve well in water. They also have a time getting into the body and they are not very stable. They have a hard time getting through the skin. There are some ways to give these agents to people that can help with these problems. These are called drug delivery systems. One kind is called microemulsions. These systems help the agents dissolve better and stay stable. They also help them get through the skin. This makes the antifungal agents work better against the fungi.

7. MICROEMULSION DRUG DELIVERY SYSTEM

Microemulsions are a unique type of "dispersion" that can seem translucent or transparent. In their research investigation to create translucent or transparent emulsion systems, medium short chain alcohols are titrated with long-chain fatty (soapy milky emulsions), Hoar and Schulman (1943) made the initial discovery of them. A thermodynamically stable, isotropically transparent mixture of two immiscible liquids, such oil and water, supported by a surfactant molecule interfacial coating is called a microemulsion (ME) [61]. They have become innovative drug delivery vehicles that enable parenteral, ocular, percutaneous, topical, transdermal, and regulated or sustained release of medication. Microemulsions typically contain uniformly distributed droplets with diameters between 10 and 100 nm. These systems have low viscosity, a high solubilizing capacity for lipophilic and amphiphilic medicines, and improved stability in comparison to traditional emulsions because of their nanoscale size. They are adaptable carriers because of their biphasic composition, which permits the addition of both hydrophilic and lipophilic medications as well as permeation enhancers [62]. Microemulsions' applications of pharmacology have been thoroughly investigated as potential medication delivery methods for medications that are poorly soluble in water. They are frequently used as drug carrier systems for topical, oral, and parenteral drug administration because to a variety of advantages, including as simplicity of synthesis, spontaneous generation and scale-up, thermodynamic stability, enhanced drug solubilization, and bioavailability [63,64]. The structure of microemulsions is shown in Figure 4.



Surfactant: forms the interfacial film
Cosurfactant: minimize interfacial stress and guarantee the interfacial layer's flexibility
Figure: -4 Structure of microemulsion

7.1. Types Of Microemulsions

Despite their thermodynamic stability, microemulsions are only present under certain conditions. There are four different kinds of equilibrium microemulsion phase, according to
Winsor; these phases are also known as Winsor phases. They are-
7.1.1. Winsor I, an oil-in-water microemulsion
7.1.2. Winsor II or water-in-oil microemulsion
7.1.3. Winsor III or bi-continuous microemulsion
7.1.4. Winsor IV or single-phase homogenous mixture

7.1.1. Winsor I, an oil-in-water microemulsion

A surfactant (and sometimes co-surfactant) film envelops the oil-in-water oil droplets type of microemulsion, creating the water-dispersed continuous internal phase. In contrast to the w/o microemulsion, this kind of microemulsion has a greater volume of interaction [65].

7.1.2. Winsor II or water-in-oil microemulsion

Water droplets are encased in a continuous oil phase in the water-in-oil. These are known as
"reversemicelles," where the polar head groups of the surfactant face the water droplets and the fatty acid tails face the oil phase. A parenterally or orally administered w/o microemulsion may become unstable due to the aqueous biological system [66].

7.1.3. Winsor III or bi-continuous microemulsion

The volumes of oil and water in a bi-continuous microemulsion systems are similar. Water as well as oil are present in this instance as a continuous phase. Oil and water are combined in an irregular channel that looks like a "spongephase." This bi-continuous condition may be traversed by transitions from o/w to w/o microemulsion. Non-Newtonian flow and plasticity are possible characteristics of bi-continuous microemulsions. These qualities make them very useful for topical or intravenous drug administration [67].

7.1.4. Winsor IV or single-phase homogenous mixture

Surfactants, water, and oil are all uniformly combined Winsor IV, a single-phase homogenous mixture . Microemulsions' classification emphasizes how adaptable they are as drug delivery methods, especially for topical applications. Herbal microemulsion systems for better antifungal therapy have been developed as a result of the increased exploration of microemulsions for the incorporation of herbal antifungal agents due to their high solubilization capacity and penetration-enhancing qualities [68].

7.2. Components Of Microemulsion

Microemulsions are developed and formulated using a variety of ingredients. Microemulsions mostly contain oil and surfactants, which must be therapeutically acceptable, nontoxic, and biocompatible.
The primary elements of a microemulsion are:

I. Oil phase
II. Aqueous phase
III. Surfactant
IV. Cosolvent

I. Oil phase

Any liquid with low polarity and low water miscibility is considered oil; examples of such phases include vegetable oil, toluene, mineral oil, cyclohexane, etc. Because it can solubilize the required dose of the lipophilic medicine and increase the amount of lipophilic drug carried by the intestinal lymphatic system, oil is one of the most important components of microemulsion [69].

II. Aqueous phase

The aqueous phase usually contains hydrophilic active ingredients and preservatives.
Sometimes buffer solutions are used as an aqueous phase [70].

III.Surfactant

A substance with some superficial or interfacial action and a surfactant is a substance that is used to lessen surface or interface tension. It is drawn to both nonpolar and polar liquids. Molecules with a polar head group and a polar tail are known as surfactants. Surfactant molecules selfassociate due to a range of intramolecular and intermolecular interactions as well as entropy concerns. For instance, because it is thermodynamically advantageous, surfactants concentrate when mixed with water close to the oil/water interaction [71]. The surfactant's molecules can organize themselves in many ways. They can produce spherical micelles, hexagonal reverse micelles, rod-shaped micelles, a hexagonal phase, and lamellar (sheet) phases. Spherical, isolated droplets with modest quantities of dispersed phase are present in the microemulsions [72].

The several kinds of surfactants that support the advancement of microemulsion systems are

- Cationic
- Anionic
- Non-ionic
- Zwitterionic surfactants.

• Cationic Surfactants

In water, cationic surfactants split into a positively charged amphiphilic ion and a counter anion, typically a halide. They frequently include nitrogen-based substances such fatty amine salts with lengthy alkyl chains and quaternary ammonium salts. Hexadecyltrimethylammonium bromide and didodecyl ammonium bromide are two examples [73].

• Anionic Surfactants

In water, anionic surfactants split into a negatively charged amphiphilic ion and a cation, such as potassium or sodium. They account for almost half of the world's surfactant production and are the most often utilized surfactants. Usually, carboxylate, sulfate, or sulfonate groups are the source of their charge [74].

• Non-ionic Surfactants

Non-ionic surfactants don't ionize in aqueous solutions. Alcohols, esters, phenols, and amides are examples of non-dissociable functional groups found in their hydrophilic groups. Polyethylene glycol chains are present in many non-ionic surfactants, which increase their water solubility [75].

• Zwitterionic Surfactants

Surfactants that are zwitterionic are molecules that have both negative and positive charges. Phospholipids like lecithin and betaine derivatives are two examples. These surfactants are frequently utilized in microemulsions and show good biocompatibility [76].

IV. Co-solvent (Co-surfactant)

Often, the oil–water interfacial tension cannot be adequately reduced by single-chain surfactants alone to create stable microemulsions. In order to improve the interfacial film's flexibility and enable the creation of microemulsions across a larger range of compositions, cosolvents or Co-surfactants are introduced. Glycols (propylene glycol), medium-chain alcohols, amines, and short-chain alcohols (ethanol, propanol, butanol), and organic acids are examples of common co-surfactants. Additionally, these substances help to stabilizing the microemulsion system by preventing the development of liquid crystalline or gel phases [77].

7.3. Mechanism Of Drug Penetration And Enhancement Of Penetration:

The skin, which is the body's outermost layer, serves mainly as a barrier that keeps viruses and other foreign substances out of the body and shields it from damaging environmental stimuli like light, temperature, and radiation. Because of the skin's protective properties, topical or transdermal medication delivery is exceedingly challenging. As a result, a number of different approaches have been used to boost medication delivery and skin absorption, such as transdermal adhesives, delivery systems, penetration enhancers, and novel drug delivery systems. By momentarily disturbing the stratum corneum of the epidermis, all of these techniques improve medication penetration [78].

Microemulsions dissolve the medication and lessen the drag force on the skin's surface. Surfactants or lipids that can disintegrate or disturb the stratum corneum's lipid bilayer structure are occasionally utilized as penetration enhancers in formulations. As a result, the layer reduces the cornea's barrier function and creates holes or channels that allow drugs to pass through the skin. Penetration enhancers allow the medication to enter the stratum corneum at a particular rate by altering the lipid bilayer and keratinocyte organization [79]. The lipid-protein partitioning theory provides the best explanation for the relationship between transmission enhancers and the stratum corneum (skin barrier). This theory states that three key factors contribute to drug penetration: 1) drug interaction with the cellular lipid bilayer; 2) drug interaction with keratinocytes; and 3) an extra solvent or intervening enhancer. Transdermal medication administration can be facilitated by reversing the skin barrier through the stratum corneum. Three key mechanisms can lead to medication release once the constriction is lessened. 1) Intracellular: Hydrophilic materials benefit from pathways between cells. 2) Intracellular: Lipophilic drugs are best transported between cells. 3) Follicular/transadnexal: medication administration via skin appendages or hair follicles [80]. The different pathways of skin penetration by microemulsions are shown in Figure 5.

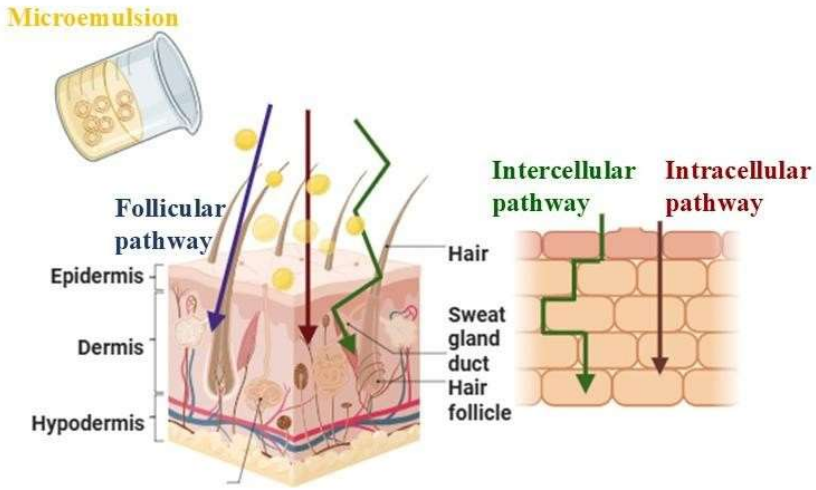


Figure: - 5 "Skin penetration pathway of microemulsion"

7.4. Advantages Of Microemulsion System: - Microemulsion systems improve drug solubility, bioavailability, and penetration due to their nanosized droplets and high stability. There are several advantages of microemulsion systems- [81-84].

- The microemulsion can be reversed. They can become erratic at high or low temperatures, but the microemulsion reforms when the temperature reaches the stability range.
- Because of their strong thermodynamic stability, microemulsions are simple to make and require no energy input.
- Thermodynamically stable, microemulsions enable the system to self-emulsify.
- Microemulsions function as drug supersolvents, solubilizing both hydrophilic and hydrophobic [lipophilic] medicines, including those that are not soluble in either hydrophobic and aqueous solvents.
- Using microemulsions as delivery methods can increase a medication's effectiveness by lowering the overall dosage and reducing side effects.
- Microemulsions have an advantage over creams in terms of improving stratum corneum hydration and medication penetration into the skin and bloodstream.
- Thermo-labile drugs don't break down and are easy to administer.
- A substantial amount of medication can be added due to the formulation's excellent solubilizing capacity, which may increase thermodynamic action towards the skin.
- The surfactant and co-surfactant in the microemulsions may reduce the diffusional barrier of the stratum corneum by acting as penetration enhancers.
- Low surface tension guarantees good skin contact. A practically constant concentration gradient across the skin can also be maintained throughout time by using the dispersed phase as a reservoir.

8. HERBAL MICROEMULSION IN ANTIFUNGAL THERAPY

In antifungal medicine, "herbal microemulsion" refers to sophisticated colloidal systems that incorporate bioactive chemicals obtained from plants to improve solubility, stability, and antifungal efficacy. In addition to providing a safer and more biocompatible substitute for traditional antifungal formulations, these systems enhance drug penetration, bioavailability, and therapeutic performance.

8.1. Reported Studies

1. Li *et al.* (2021) prepared a microemulsion formulation of *Waltheria indica* extract with flavonoids, alkaloids, tannins, and terpenoids. The formulation demonstrated improved permeability, good stability, and an appropriate droplet size. By compromising the integrity of the fungal cell membrane and modifying enzymes linked to oxidative stress, the study showed substantial antifungal activity against *Phytophthora capsica,* suggesting its potential as a plant-based antifungal system [85].

2. Nguyen *et al.* (2022) prepared a microemulsion system incorporating *Citrus hystrix* (kaffir lime) leaf oil rich in citronellal, limonene, and terpenoids. The formulation demonstrated enhanced solubility of the active ingredients, nano-sized droplets, and high physical stability. Strong antifungal activity against *Aspergillus niger, Trichophyton species,* and *Candida albicans* demonstrated its efficacy in treating dermatophytic infections [86].

3. Khan *et al.* (2023) formulated a microemulsion-based gel of *Thymus vulgaris* (thyme oil), containing bioactive compounds such as thymol and carvacrol. It helps medicine get into the skin better. Release it properly. This results in it working well against certain fungus infections like *Candida* and *Trichophyton*. This suggests it could be a way to make a medicine that you put on your skin to fight fungus [87].

4. Sharma et al. (2020) developed a *herbal* microemulsion incorporating essential oil of *Ocimum sanctum* for topical antifungal application. It helps the drug

get into the skin better. Keeps releasing it over time. The new mixture worked better than the herbal things we use. It got into the skin. Stayed there longer. The study showed that it was really good, at fighting a type of fungus called *Candida albicans* and other fungi that affect the skin. The mixture was also very stable. People liked using it because it did not feel greasy on the skin and was easy to put on. Sharma and his team found that the herbal microemulsion was a way to fight fungus on the skin [88].

5. Chen *et al.* (2015) formulated an essential oil-based microemulsion incorporating tea tree oil rich in terpinen-4-ol. They used tea tree oil that had a lot of terpinen-4-ol in it. This mixture had small drops and was very stable. It also helped the oil spread out better. The study found that this mixture was very good at fighting fungi like *Candida albicans* and *Trichophyton rubrum*. This was because the good stuff in the mixture could get to where it needed to go and work better [89].

6. Toledo et al. (2020) developed a herbal microemulsion loaded with essential oil of *Cymbopogon nardus* for topical antifungal application. This mixture was for putting on the skin to fight fungus. The mixture helped the good stuff in the herb get into the skin better. It stayed in the body for a longer time. This study showed that the mixture was really good at fighting a type of fungus called *Candida albicans*. It worked well in tests with cells and with living things. The mixture was also better, than using the oil from
the herb. It did not go bad as easily. It did not evaporate as quickly. This made the herb work better to help people [90].

8.2. Comparative Efficacy

The comparative evaluation of herbal microemulsion and synthetic antifungal formulations, based on parameters such as source, mechanism of action, drug delivery efficiency, safety, resistance development, and therapeutic outcomes, is summarized in Table 4.

Table: -4 Comparative efficacy

Parameter	Herbal Microemulsion Formulation	Synthetic Antifungal Formulation
Source of Active Ingredient	Obtained from botanical extracts, essential oils, and phytochemicals like neem oil, tea tree oil, turmeric, and aloe vera	Made up of chemically produced antifungal substances like ketoconazole, clotrimazole, terbinafine, and nystatin [91]
Mechanism of Action	Various mechanisms such as damaging fungal cell membranes, suppressing fungal growth, exhibiting antioxidant properties, and providing antiinflammatory effects	Primarily focus on particular fungal pathways like blocking ergosterol production or inhibiting squalene epoxidase [92]
Drug Delivery Efficiency	Microemulsion droplets boost the solubilization of hydrophobic phytochemicals while enhancing skin absorption and bioavailability	Traditional creams or gels might exhibit restricted absorption and reduced solubility for lipophilic medications [93]
Safety Profile	Typically more secure with low toxicity and reduced side effects because of its natural source	May lead to irritation, a burning feeling, allergic responses, and systemic effects with extended use [94]
Resistance Development	Reduced likelihood of resistance because various bioactive compounds work together synergistically	Frequent use of single-target medications may result in fungal resistance [95]
Additional Therapeutic Effects	Provide additional benefits such as antioxidant, anti-inflammatory, wound healing, and moisturizing effects	Primarily antifungal with limited additional therapeutic benefits [96]
Onset of Action	Sometimes slower due to natural compounds but effective with sustained use	Rapid antifungal action due to potent synthetic drugs [97,98]
Patient Acceptability	Chosen for its natural origin and gentle impact on the skin	Occasionally constrained because of discomfort or negative responses [99]

9. CHARACTERIZATION TECHNIQUES

9.1. Physical appearance

Looking at the microemulsion helps us see what it looks like. We check if it is clear, transparent and if all parts are well mixed. A good microemulsion should look clear. Not separate into different parts. This means the microemulsion is stable and well mixed [100].

9.2. Zeta potential

Zeta potential is used to check if the microemulsion is stable. The HORIBA SZ-100 helps find out the surface charge of the particles by measuring the Zeta potential of the microemulsions. To do this we put the sample in a single-use cell. Then we measure how the particles move in a field to find the Zeta potential [101].

9.3. Droplet Size and Size Distribution

One important factor affecting stability, medication release, and bioavailability is droplet size. Dynamic light scattering (DLS) is typically used to measure it. Microemulsions usually show uniform distribution with droplet sizes between 10 and 100 nm and a low polydispersity index (PDI) [102].

9.4. FTIR spectroscopy

Potential drug-excipient interactions can be found using Fourier Transform Infrared (FTIR) spectroscopy. The KBr pellet method is used to prepare the sample, which is compressed under high pressure and scanned throughout a wavelength range of 4000 to 400 cm^{-1}. Any alteration or shift in the formulation's characteristic peaks suggests potential interactions [103].

9.5. Measurement of pH

Using a calibrated pH meter (Digital Potentiometer Model EQ-601 Equip-Tronics), the electrode was submerged directly into the dispersion to determine the pH values of the improved formulation [104].

9.6. Viscosity measurement

Low viscosity systems are often micro emulsions. Using a Brookfield viscometer and LV spindle number 63, the produced micro emulsion's viscosity was tested at 25°C and 60 rpm [105].

9.7. Drug stability

The optimal microemulsion is stored at room temperature, at 50 ± 2 °C, and under cold temperatures (4–8 °C). The microemulsion can be examined for phase separation, percent transmittance, globule size, and percent assay after every two months [106].

9.8. Differential scanning calorimetry (DSC)

An essential assessment method for identifying potential drug-excipient interactions is thermal analysis. Any change in the thermogram can be used to identify such an interaction. A DSC thermogram (PerkinElmer 4000, PYRIS Version-11.1.0.0488, 2009, PerkinElmer, Inc.) for the pure drug and prepared microemulsion was obtained after about 1 mg of the sample was sealed in an aluminum pan and heated at a rate of 10 °C/min, covering a temperature range of 30 °C to 300 °C under a nitrogen atmosphere at a flow rate of 20 ml/min) [107].

9.9. Dilution test:

The purpose of the dilution test is to verify the microemulsion's stability and kind. A stable microemulsion should exhibit no phase separation or cracking when diluted with the continuous phase, indicating its thermodynamic stability [108].

9.10. Transmission electron microscopy (TEM) study.

The tiny drops of microemulsion are looked using a special tool called transmission electron microscopy. This tool helps us see the details of the microemulsion by showing us the size, shape and how the tiny drops are spread out [109].

9.11. Determination of drug Content

We take an amount of microemulsion and mix it with a liquid like methanol. Then we add liquid to make it dilute so we can figure out how much medicine is, in it. To make sure the medicine is spread evenly throughout the microemulsion by using UV spectrophotometer to measure how much light is absorbed at a wavelength [110].

9.12. Refractive index

To figure out the index of the microemulsion a small drop of the microemulsion is put on the slide of an Abbe refractometer. The Abbe refractometer is set at 25°C. This helps us see if the microemulsion is really mixed well and if it looks the same in all directions [111].

9.13. In-vitro drug release

A Franz diffusion cell helps to test how a drug is released in the body. The Franz cell has two parts: a receptor compartment and a donor compartment. The receptor part has a liquid that works like the body fluids. The donor part holds the drug in a liquid form called microemulsion. The two parts are separated by a membrane. To understand how the drug is released we take samples at set times. These samples are then checked using UV spectrophotometer. The Franz diffusion cell is useful, for finding out how a drug behaves. The drug release profile shows how much of the drug is released over time. The diffusion behavior shows how the drug moves through the membrane [112].

10. CHALLENGES

The use of microemulsion systems for antifungal medication is limited by several issues despite their potential. One major concern is the stability of compounds. Many herbal compounds, such as terpenoids and flavonoids are sensitive to light, temperature, oxygen and pH. This sensitivity can reduce the stability and effectiveness of the formulation. Herbal microemulsion systems need a balance of ingredients. This balance includes oil phase, surfactants, co-surfactants and aqueous phase. Finding the balance is a

challenge. Prolonged use of microemulsion systems on the skin can cause irritation or hypersensitivity. This is due to the concentration of surfactants required for microemulsion production. The chemical makeup of extracts can vary. This variation is caused by differences in plant source growing conditions and extraction methods. As a result, the therapeutic results of microemulsion systems can be inconsistent.

Most research on microemulsion systems is limited to laboratory studies. There are studies, on animals and humans. For herbal microemulsion systems to be developed into medicines several obstacles must be overcome. These obstacles include approval, standardization of herbal extracts and large-scale production while maintaining formulation stability [114].

11. FUTURE PERSPECTIVES

Herbal microemulsion systems are interesting ways to deliver antifungal therapy. These systems have gotten a lot of attention because they can help make medication more stable and release it in a controlled way. In the future researchers might look into combining microemulsion systems with other tiny systems like nanoemulgels, liposomes, solid lipid nanoparticles and nanostructured lipid carriers to make antifungal drugs work better [115].

Another cool idea is to make gel formulations that use microemulsions or emulgels which bring together the good things about gels and herbal microemulsions to make them thicker, easier to spread and better at staying on the skin, which can make antifungal therapy work better when you put it on your skin. Herbal microemulsion systems have been studied a lot for delivering medication to the skin. These systems can hold components and make them more stable and they can release medication over a longer time. Compared to the ways of making medication herbal microemulsion systems can make herbal medicines work better when you put them on your skin by helping the active components get through the outer layer of skin [116].

Also looking into antifungal chemicals from plants and putting them into better herbal microemulsion systems might give us safer and more powerful alternatives to traditional antifungal medications. We might be able to overcome antifungal medication resistance by combining antifungal drugs with natural herbal components to make them work together. Moreover, to get these microemulsion systems approved and made on a big scale we need to standardize the herbal extracts and make rules, for quality control [117].

12. CONCLUSION

Fungal infections are a problem because they are happening a lot and they are getting harder to treat with the usual medicines. This is a health concern worldwide. The thing is, many of the medicines we use to treat infections are not very good. They can be bad, for us they do not work well and they can even help create new kinds of fungi that are hard to kill. Fungal infections are a problem because many antifungal medicines have limitations. These limitations include being toxic not being absorbed well by the body and not being able to be dissolved. Also new fungus strains are developing. All these problems show that we need to find ways to treat fungal infections. We need to make treatments more effective. One way to do this is to use microemulsion-based drug delivery systems to help fight infections.

Microemulsions can improve medication solubility, stability and skin penetration. Microemulsions have advantages over traditional carriers. They work well with both water loving and fat-loving chemicals. They can dissolve substances and are easy to make. They are also very stable. Adding bioactive components to microemulsion systems can make antifungal treatments more effective. It can also reduce toxicity. Improve skin penetration. Herbal microemulsion formulations show promise for creating more effective topical antifungal treatments. However more research and testing are needed to make these treatments a reality. Further investigation and clinical validation are required for their use in medicine. This includes refining the formulations to ensure they are safe and effective. Then can herbal microemulsion based treatments become a practical solution, for fungal infections.

REFERENCES

1. Denning, D.W., 2024. Global incidence and mortality of severe fungal disease. Lancet Infect. Dis. 24, e428–e438. https://doi.org/10.1016/S1473-3099(23)00692-8.
2. Reddy GKK, Padmavathi AR, Nancharaiah YV. Fungal infections: Pathogenesis, antifungals and alternate treatment approaches. Curr Res Microb Sci. 2022 Apr 27;3:100137. doi: 10.1016/j.crmicr.2022.100137. PMID: 35909631; PMCID: PMC9325902.
3. Verma S, Madhu R. The Great Indian Epidemic of Superficial Dermatophytosis: An Appraisal. Indian J Dermatol. 2017; 62:227–236 https://doi.org/10.4103/ijd.IJD_206_17 PMID: 28584364
4. Z. Hu, et al., Sanguinarine, Isolated From Macleaya cordata, Exhibits Potent Antifungal Efficacy Against Candida albicans Through Inhibiting Ergosterol Synthesis, Front. Microbiol. 13 (2022) http://doi.org/10.3389/fmicb.2022.908461.
5. Fung, S.; Shirley, M. Rezafungin: A Review in Invasive Candidiasis. Drugs 2025, 85, 415–423. [CrossRef]
6. Kim, J.H., Cheng, L.W., Chan, K.L., Tam, C.C., Mahoney, N., Friedman. M., Shilman, M.M., Land, K.M., 2020. Antifungal drug repurposing. Antibiotics (Basel). 9(11), 812. [DOI] [PMC free article] [PubMed]
7. Khurana A, Sharath S, Sardana K, Chowdhary A. Clinico-mycological and therapeutic updates on cutaneous dermatophytic infections in the era of Trichophyton indotineae. J Am Acad Dermatol. 2024; 91:315–323. https://doi.org/10.1016/j.jaad.2024.03.024
8. Kashyap VH, Mishra A, Bordoloi S, Varma A, Joshi NC. Exploring the intersection of Aspergillus fumigatus biofilms, infections, immune response and

antifungal resistance. Mycoses 2023;66:737-754
9. Auxier B, Debets AJM, Stanford FA, Rhodes J, Becker FM, Reyes Marquez F, et al. The human fungal pathogen Aspergillus fumigatus can produce the highest known number of meiotic crossovers. PLoS Biol 2023;21: e3002278
10. Cao Q, Ge C, Wang X, Harvey PJ, Zhang Z, Ma Y, et al. Designing antimicrobial peptides using deep learning and molecular dynamic simulations. Brief Bioinform 2023; 24:bbad058
11. L. Brown, A. K. Leck, M. Gichangi, M. J. Burton, and D. W. Denning, "The Global Incidence and Diagnosis of Fungal Keratitis," Lancet Infectious Diseases 21, no. 3 (2021): e49–e57, https://doi.org/10.1016/S1473- 3099(20)30448-5
12. Kwizera R, Abdolrasouli A, Garcia-Effron G, Denning DW. Antifungal susceptibility testing: applicability of methods and strategies for improving access in resourceconstrained settings. Lancet Infect Dis. 2024. https://doi.org/10.1016/S14733099(24)00429-8 PMID: 39305909.
13. Abd Elaziz, D.; Abd El-Ghany, M.; Meshaal, S.; El Hawary, R.; Lotfy, S.; Galal, N.; Ouf, S.A.; Elmarsafy, A. Fungal infections in primary immunodeficiency diseases. J. Clin. Immunol. 2020, 219, 108553. [CrossRef]
14. N. Sharma, B. Bagga, and D. Singhal, "Fungal Keratitis: A Review of Clinical Presentations, Treatment Strategies and Outcomes," Ocul Surf 24 (2022): 22–30, https://doi.org/10.1016/j.jtos.2021.12.001.
15. Marcos, C.M., de Oliveira, H.C., de Melo, W.C., da Silva, J.F., Assato, P.A., Scorzoni, L., Rossi, S.A., de Paula, E. Silva.A.C., Mendes-Giannini, M.J., Fusco-Almeida, A.M., 2016. Anti-immune strategies of pathogenic fungi. Front. Cell. Infect. Microbiol. 6, 142.
16. Seidel, D.; Wurster, S.; Jenks, J.D.; Sati, H.; Gangneux, J.P.; Egger, M.; AlastrueyIzquierdo, A.; Ford, N.P.; Chowdhary, A.; Sprute, R.; et al. Impact of climate change and natural disasters on fungal infections. Lancet Microbe 2024, 5, e594–e605. [CrossRef]
17. Hokken, M.W.J., Zwaan, B.J., Melchers, W.J.G., Verweij, P.E., 2019. Facilitators of adaptation and antifungal resistance mechanisms in clinically relevant fungi. Fungal Genet. Biol. 132, 103254. https://www.cdc.gov/fungal/awareness-week.html. Accessed on 31/12/2021.
18. Strickland, A.B.; Shi, M. Mechanisms of fungal dissemination. Cell. Mol. Life Sci. 2021, 78, 3219–3238. [CrossRef] [PubMed]
19. Mittal, J.; Ponce, M.G.; Gendlina, I.; Nosanchuk, J.D. Histoplasma capsulatum: Mechanisms for pathogenesis. Fungal Physiol. Immunopathogenesis 2019, 422, 157– 191.
20. Kainz, K.; Bauer, M.A.; Madeo, F.; Carmona-Gutierrez, D. Fungal infections in humans: The silent crisis. Microb. Cell 2020, 7, 143. [CrossRef]
21. Nami, S.; Mohammadi, R.; Vakili, M.; Khezripour, K.; Mirzaei, H.; Morovati, H. Fungal vaccines, mechanism of actions and immunology: A comprehensive review. Biomed. Pharmacother. 2019, 109, 333–344. [CrossRef]
22. Almeida, F.; Rodrigues, M.L.; Coelho, C. The still underestimated problem of fungal diseases worldwide. Front. Microbiol. 2019, 10, 214. [CrossRef]
23. Kabashima K, Honda T, Ginhoux F, Egawa G. The immunological anatomy of the skin. Nat Rev Immunol. 2019;19(1):19-30.
24. Kashem SW, Kaplan DH. Skin immunity to Candida albicans. Trends Immunol. 2016;37(7):440-450.
25. Iliev ID, Leonardi I. Fungal dysbiosis: immunity and interactions at mucosal barriers. Nat Rev Immunol. 2017;17(10):635-646.
26. Bacher P, Hohnstein T, Beerbaum E, et al. Human anti-fungal Th17 immunity and pathology rely on cross-reactivity against Candida albicans. Cell. 2019;176(6):13401355.e1315.
27. Haghani, I.; Babaie, M.; Hoseinnejad, A.; Rezaei-Matehkolaei, A.; Mofarrah, R.; Yahyazadeh, Z.; Kermani, F.; Javidnia, J.; Shokohi, T.; Azish, M.; et al. High prevalence of Terbinafine Resistance among Trichophyton mentagrophytes/T. Interdigitale Species Complex, a cross-sectional study from 2021 to 2022 in Northern Parts of Iran. Mycopathologia 2024, 189, 52. [CrossRef]
28. Wang S, Pan J, Gu L, Wang W, Wei B, Zhang H, Chen J, Wang H. Review of treatment options for a multidrug-resistant fungus: Candida auris. Med Mycol. 2024 Jan 09;62(1) [PubMed]
29. Caplan AS, Todd GC, Zhu YC, Sikora M, Akoh CC, Jakus J, et al. Clinical Course, Antifungal Susceptibility, and Genomic Sequencing of Trichophyton indotineae. JAMA Dermatol. 2024; 12208:1–9. https:// doi.org/10.1001/jamadermatol.2024.1126
30. Balcerek, M.I.; Stewart, A.G.; Chapman, P.; Lazarus, S. Reducing the off-target endocrinologic adverse effects of azole antifungals—Can it be done? Int. J. Antimicrob. Agents 2022, 59, 106587. [CrossRef] [PubMed]
31. Shafiei, M., Peyton, L., Hashemzadeh, M., Foroumadi, A., 2020. History of the development of antifungal azoles: a review on structures, SAR, and mechanism of action. Bioorg. Chem. 104, 104240. https://doi.org/10.1016/j.bioorg.2020.104240.
32. Viecceli C, Mattos ACV, Hirakata VN, Garcia SP, Rodrigues TDC, Czepielewski MA. Ketoconazole as second-line treatment for Cushing's disease after transsphenoidal surgery: systematic review and meta-analysis. Front Endocrinol (Lausanne). 2023;14:1145775. [PMC free article] [PubMed]
33. Czajka, K.M., Venkataraman, K., Brabant-Kirwan, D., Santi, S.A., Verschoor, C., Appanna, V.D., Singh, R., Saunders, D.P., Tharmalingam, S., 2023.

Molecular mechanisms associated with antifungal resistance in pathogenic candida species. Cells 12, 2655. https://doi.org/10.3390/cells12222655
34. Lee, Y., Robbins, N., Cowen, L.E., 2023. Molecular mechanisms governing antifungal drug resistance. NPJ Antimicrob. Resist. 1, 5. https://doi.org/10.1038/s44259-023- 00007-2
35. Tang, K. W. K., Millar, B. C., & Moore, J. E. (2023). Antimicrobial resistance (AMR). British Journal of Biomedical Science, 80, 11387.
36. Gregor, J.B., Gutierrez-Schultz, V.A., Hoda, S., Baker, K.M., Saha, D., Burghaze, M.G., Vazquez, C., Burgei, K.E., Briggs, S.D., 2023. An expanded toolkit of drug resistance cassettes for candida glabrata, candida auris, and candida albicans leads to new insights into the ergosterol pathway. mSphere 8. https://doi.org/10.1128/ msphere.00311-23.
37. Ivanov, M., Ciri ´ ´c, A., Stojkovi´c, D., 2022. Emerging antifungal targets and strategies. Int. J. Mol. Sci. 23, 2756. https://doi.org/10.3390/ijms23052756.
38. Szymanski, ´ M., Chmielewska, S., Czyzewska, ˙ U., Malinowska, M., Tylicki, A., 2022. Echinocandins – structure, mechanism of action and use in antifungal therapy. J. Enzyme Inhib. Med. Chem. 37, 876–894. https://doi.org/10.1080/ 14756366.2022.2050224.
39. Al Shaer D, Al Musaimi O, Albericio F, de la Torre BG. 2023 FDA TIDES (Peptides and Oligonucleotides) Harvest. Pharmaceuticals (Basel). 2024 Feb 13;17(2) [PMC free article] [PubMed] [Reference list]
40. Vitiello, A., Ferrara, F., Boccellino, M., Ponzo, A., Cimmino, C., Comberiati, E., et al. (2023). Antifungal drug resistance: An emergent health threat. Biomedicines, 11(4), 1063.
41. Vu, B.G., Stamnes, M.A., Li, Y., Rogers, P.D., Moye-Rowley, W.S., 2021. The candida glabrata Upc2A transcription factor is a global regulator of antifungal drug resistance pathways. PLoS Genet. 17, e1009582. https://doi.org/10.1371/journal. pgen.1009582.
42. Sigera, L.S.M., Denning, D.W., 2023. Flucytosine and its clinical usage. Ther. Adv. Infect. Dis. 10. https://doi.org/10.1177/20499361231161387.
43. Hou˘st’, J., Spí˘zek, J., Havlí˘cek, V., 2020. Antifungal drugs. Metabolites 10, 106. https:// doi.org/10.3390/metabo10030106
44. Chaachouay N, Zidane L. Plant-derived natural products: A source for drug discovery and development. Drugs Drug Candidates 2024;3:184-207
45. Carmo, A., Rocha, M., Pereirinha, P., Tom´e, R., Costa, E., 2023. Antifungals: from pharmacokinetics to clinical practice. Antibiotics 12, 884. https://doi.org/10.3390/ antibiotics12050884.
46. Cowen LE, Sanglard D, Howard SJ, Rogers PD, Perlin DS. Mechanisms of antifungal drug resistance. Cold Spring Harb Perspect Med. 2021;11(7):a019752.
47. Choy, H.L., Gaylord, E.A., Doering, T.L., 2023. Ergosterol distribution controls surface structure formation and fungal pathogenicity. mBio. https://doi.org/10.1128/ mbio.0135
48. Carolus, H., Pierson, S., Lagrou, K., Van Dijck, P., 2020. Amphotericin B and other polyenes—discovery, clinical use, mode of action and drug resistance. J. Fungi 6, 321. https://doi.org/10.3390/jof6040321
49. Kaushik K, Agarwal S. Role of herbal antifungal agents for the management of fungal diseases: A systematic review. Asian Journal of Pharmaceutical and Clinical Research. 2019;12(7):34–40. https://doi.org/10.22159/ajpcr.2019.v12i7.33831
50. Hsu H, Sheth CC, Veses V. Herbal extracts with antifungal activity against Candida albicans: A systematic review. Mini Reviews in Medicinal Chemistry. 2021;21(1):90– 117.
51. Gucwa K, Milewski S, Dymerski T, Szweda P. 2018. Investigation of the Antifungal Activity and Mode of Action of Thymus vulgaris, Citrus limonum, Pelargonium graveolens, Cinnamomum cassia, Ocimum basilicum, and Eugenia caryophyllus Essential Oils. 5. Molecules 23:1116
52. Yazgan H. 2020. Investigation of antimicrobial properties of sage essential oil and its nanoemulsion as antimicrobial agent. LWT 130:109669
53. Dellavalle PD, Cabrera A, Alem D, Larrañaga P, Ferreira F, Rizza MD. Antifungal activity of medicinal plant extracts against phytopathogenic fungus alternaria spp. Chilean journal of agricultural research, 2011; 71(2): 231-39.
54. Shrivastava DK, Swarnkar K. Antifungal Activity of leaf extract of Neem (Azadirachta Indica Linn). Int.J.Curr. Microbiol. App. Sci, 2014; 3(5): 305-08.
55. Kaur N, Bains A, Kaushik R, Dhull SB, Melinda F, Chawla P. A Review on Antifungal Efficiency of Plant Extracts Entrenched Polysaccharide-Based Nanohydrogels. Gels. 2021;7(3):112. PMCID: PMC8232670; PMID: 34203999
56. El-Bondkly EAM, Al Shammari B, El-Gendy MMAA, Alsafari IA, El-Bondkly AAMA, El-Shenawy FS, et al. Phytochemical screening, antifungal, and anticancer activities of medicinal plants Thymelaea hirsuta, Urginea maritima, and Plantago albicans. Biomed Res Int 2022; 2022:9544915
57. Javaid A, Rehman HA. Antifungal activity of leaf extracts of some medicinal trees against Macrophomina phaseolina. Journal of Medicinal Plants Research, 2011; 5(13): 2868-72.
58. Kaur N, Bains A, Kaushik R, Dhull SB, Melinda F, Chawla P. A Review on Antifungal Efficiency of Plant Extracts Entrenched Polysaccharide-Based Nanohydrogels. Gels. 2021;7(3):112. PMCID: PMC8232670; PMID: 34203999
59. Bonzi S, Somda I, Zida EP, Sérémé P. In vitro Antifungal Activity of Various Local Plant Extracts in the Control of Phoma sorghina (Sacc.) Boerema et

al. and Colletotrichum graminicola (Ces.) Wilson, as Sorghum Seed Mold Pathogen in Burkina Faso. Tropicultura, 2012; 30(2): 103-06
60. Pumival P, Tadtong S, Athikomkulchai S, Chittasupho C. Antifungal Activity and the Chemical and Physical Stability of Microemulsions Containing Citrus hystrix DC Leaf Oil. Natural Product Communications. 2020;15(9). doi:10.1177/1934578X20957755
61. Gandhi JV, Suthar DJ, Patel HK, Shelat PK, Parejiya PJ. Design, fabrication, and evaluation of microemulsion based gel of essential oil of Thymus vulgaris for superficial fungal infections. International Journal of Pharmaceutical Sciences and Drug Research. 2020;12(2):110–118. doi:10.25004/IJPSDR.2020.120214
62. Abd Rashed, A., Rathi, D.-N. G., Ahmad Nasir, N. A. H., Abd Rahman, A. Z. Antifungal Properties of Essential Oils and Their Compounds for Application in Skin Fungal Infections: Conventional and Nonconventional Approaches. Molecules 2021, 26 (4), 1093. https://doi. org/10.3390/molecules26041093
63. Nanomaterials. 2020;10(8):1657. Ben Miri Y, Aazza S, Bouslamti R, Ennabili A, Alabdul Magid A. Essential oils: chemical composition and diverse biological activities – a comprehensive review. Front Pharmacol. 2022;12:723233. doi:10.3389/fphar.2021.723233
64. Ben Miri Y, et al. Essential oils: Chemical composition and diverse biological activities— A comprehensive review. Front Pharmacol. 2025;16:723233.
65. Suhail N, Alzahrani AK, Basha1 WJ, Kizilbash N, Zaidi A, Ambreen J, et al. Microemulsions: Unique Properties, Pharmacological Applications, and Targeted Drug Delivery. Front Nanotechnol. 2021; 3: 1-6.
66. Bhavani, Jeeva, Karthick, Raghul, Pravin Kumar, Vijay. A Review on formulation and evaluation of microemulsion. IJPRA Journal. 2022; 7: 1644
67. Navneet Kumar Verma et al.; Topical Micro emulsions and it's Application - A Review. EAS J Pharm Pharmacol; 2020;2(2):36-45.
68. E. Mohyaldinn, M., M. Hassan, A., A. Ayoub, M. Application of Emulsions and Microemulsions in Enhanced Oil Recovery and Well Stimulation. In Microemulsion - a Chemical Nanoreactor IntechOpen, 2019. https://doi.org/10.5772/ intechopen.84538
69. Gunarto, C., Ju, Y.H., Putro, J.N., Tran-Nguyen, P.L., Soetaredjo, F.E., Santoso, S.P., Ayucitra, A., Angkawijaya, A.E., and Ismadji, S., 2020, Effect of a nonionic surfactant on the pseudoternary phase diagram and stability of microemulsion, J. Chem. Eng. Data, 65 (8), 4024–4033.
70. Cho W, Kim MS, Kim JS, Park J, Park HJ and Cha KH: Optimized formulation of solid self-microemulsifying sirolimus delivery systems. International Journal of Nanomedicine 2013; 8: 1673.
71. Arredondo-Ochoa, T., & Silva-Martínez, G. A. (2022). Microemulsion based nanostructures for drug delivery. Frontiers in Nanotechnology, 3. https://www.frontiersin.org/articles/10.3389/fnano.2021.753947.
72. Benbow T, Campbell J. Microemulsions as transdermal drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs): a literature review. Drug Dev Ind Pharm. 2019;45(12):1849-55. doi: 10.1080/03639045.2019.1680996, PMID 31617433.
73. PATEL TB, Patel TR, Suhagia BN. Preparation, characterization, and optimization of microemulsion for topical delivery of itraconazole. J. drug deliv. ther. 2018;8(2):136-45.
74. Alkrad JA, Assaf SM, Hussein-Al-Ali SH, Alrousan R (2022) Microemulsions as nanocarriers for oral and transdermal administration of Enoxaparin. J Drug Deliv Sci Technol 70:103248
75. Bhonge A, Bakade BV. Design, development and evaluation of microemulsion for topical drug delivery system using model drug. Journal of Pharmaceutical Research and Applications. 2024; ISSN: 2379-089X. Published June 30, 2024.
76. Faizi Muzaffar, UK Singh. Design development and evaluation of topical microemulsion. Int Res J Pharm 2017;8:95-110
77. A. E. Karadağ, N. Ü. Okur, B. Demirci, and F. Demirci, "Rosmarinus officinalis L. essential Oil Encapsulated in New Microemulsion Formulations for Enhanced Antimicrobial Activity," Journal of Surfactants and Detergents 25, no. 1 (2022): 95–103, https://doi.org/10.1002/jsde.12549.
78. Guo L. 1, Ya-Qian Fang 1, Xian-Rui Liang 2, Yu-Yan Xu. Influence of polysorbates (Tweens) on structural and antimicrobial properties for microemulsions. Int J Pharm. 2020;30(590):119939. doi: 10.1016/j.ijpharm.2020.119939.
79. Gunarto, C., Hsu, H.Y., Go, A.W., Santoso, S.P., Truong, C.T., Ju, Y.H., and Angkawijaya, A.E., 2021, Effect of cellulose nanocrystal supplementation on the stability of castor oil microemulsion, J. Mol. Liq., 325, 115181.
80. Walekar SS, Wankkhade NB. Microemusion based gel system: anovel approach for topical drug delivery. Int J Adv Pharm Sci 2014;5:1776-82.
81. Thorat YS, Kote NS, Patil VV, Hosmani AH. Formulation and evaluation of microemulsion containing neem seed oil. International Journal of Current Pharmaceutical Research. 2020;12(3):31–36. https://doi.org/10.22159/ijcpr.2020v12i3.38301
82. Barakoti H, Choudhury A, Dey BK. An Outlook for a Novel Approach: Self-Micro Emulsifying Drug Delivery System (SMEDDS). Research Journal of Pharmacy and Technology 2019; 12(4): 2055-64.
83. Koli AR, Ranch KM, Patel HP, Parikh RK, Shah DO, Maulvi FA (2021) Oral bioavailability improvement

of felodipine using tailored microemulsion: surface science, ex vivo and in vivo studies. Int J Pharm 596:120202
84. T. Shukla et al. Biomedical applications of microemulsion through dermal and transdermal route. Biomedicine & Pharmacotherapy 2018;108:1477–149
85. El-Houssieny BM, Hamouda HM, Samaha MW. Development and evaluation of clotrimazole microemulsion for topical delivery. Drug Discov Ther. 2010;4(4):287–293.
86. Chen H, Chang X, Weng T, Zhao X, Gao Z, Yang Y, et al. A study of microemulsion systems for transdermal delivery of tea tree oil. Colloids Surf B Biointerfaces. 2015;125:110–116.
87. Kaur IP, Kakkar S. Topical delivery of antifungal agents using microemulsion systems: formulation and evaluation of ketoconazole microemulsion. J Drug Deliv Sci Technol. 2018;44:265–272.
88. Khan A, Ahmad A, Akhtar F, Yousuf S, Xess I, Khan LA, Manzoor N. Ocimum sanctum essential oil and its active principles exert antifungal activity by disrupting ergosterol biosynthesis and membrane integrity. Res Microbiol. 2010;161(10):816–823. doi:10.1016/j.resmic.2010.09.008
89. Nguyen TT, Tran PH, Nguyen TH. Development of kaffir lime (Citrus hystrix) oil microemulsion for antifungal applications. Ind Crops Prod. 2022;182:114899.
90. Toledo LG, Ramos MAS, da Silva PB, Rodero CF, Gomes VS, da Silva AN, et al. Improved in vitro and in vivo anti-Candida albicans activity of Cymbopogon nardus essential oil by its incorporation into a microemulsion system. Int J Nanomedicine. 2020;15:10481–10497. doi:10.2147/IJN.S275258.
91. Iman M, Mojra M. Formulation and evaluation of neem oil nanoemulsion for antifungal activity against Trichophyton rubrum. Metall Mater Eng. 2024;30(1):XX–XX.
92. Çevikelli T, Onan D, Güven UM, Demirtürk E (2020) Preparation, characterization and invitro evaluation of Theophylline loaded microemulsion formulations. J Pharm Technol 1(1):7–12
93. Maroof K, Lee RF, Siow LF, Goh BH, Chen KF, Gan SH (2023) A new stable and bioactive formulation of Geniotrigona thoracia propolis microemulsion for oral delivery. Food Chem Adv 3:100514
94. Fan X, et al. Rosemary (Rosmarinus officinalis) essential oil microemulsion for antifungal therapy. [Journal details via PubMed]. 2025.
95. Sharma G, Thakur K, Raza K, Katare OP. Nanoemulsions and microemulsions for topical delivery of antifungal phytoconstituents: recent advances. J Drug Deliv Sci Technol. 2021;61:102110.
96. Zainal Abidin SN, et al. Herbal-based nanoformulations for antifungal therapy: recent trends and future perspectives. Pharmaceutics. 2022;14(6):1150.
97. Gupta AK, Versteeg SG. Topical antifungal agents: current and future perspectives. Drugs. 2021;81(7):813–830.
98. Nazzaro F, Fratianni F, Coppola R, Feo VD. Essential oils and antifungal activity: mechanisms and applications. Microorganisms. 2020;8(3):1–18.
99. Rai M, Ingle AP, Pandit R, Paralikar P, Shende S. Emerging role of plant-based antifungal agents and their nanoformulations. Biotechnol Adv. 2021;44:107–134.
100. Bhattacharya R, Sharma P, Bose D, et al. Synergistic potential of α-phellandrene combined with conventional antifungal agents against Candida albicans. CABI Agric Biosci. 2024;5:17
101. Cho E, Acosta K, Henkin J, et al. Synergistic antifungal effects of botanical extracts against Candida albicans. PLoS One. 2026;21(1):e0340665
102. Donkor MN, Donkor AM, Mosobil R. Combination therapy: synergism among plant extracts against pathogens. BMC Res Notes. 2023;16:83.
103. Khwaza V, Aderibigbe BA. Antifungal activities of natural products and their hybrid molecules. Pharmaceutics. 2023;15(12):2673
104. Dev A, Dwivedi J, Momin M. Formulation and characterization of acyclovir based topical microemulsions by QBD approach. J. drug deliv. ther. 2019;9(1):237-43.
105. Khumpirapang, N., Klayraung, S., Tima, S., & Okonogi, S. (2021). Development of Microemulsion Containing Alpinia galanga Oil and Its Major Compounds: Enhancement of Antimicrobial Activities. Pharmaceutics, 13(2), 265.
106. Lu, W.-C., Huang, D.-W., Wang, C.-C. R., Yeh, C.-H., Tsai, J.-C., Huang, Y.-T., & Li, P.-H. (2018). Preparation, characterization, and antimicrobial activity of nanoemulsions incorporating citral essential oil. Journal of Food and Drug Analysis, 26(1), 82-89. doi: https://doi.org/10.1016/j.jfda.2016.12.018
107. Maqsood, I., Masood, M. I., Nawaz, H. A., Shahzadi, I., & Arslan, N. (2019). Formulation, characterization and in vitro evaluation of antifungal activity of Nystatin micro emulsion for topical application. Pak J Pharm Sci, 32(4), 1671-1677.
108. Pumival, P., Tadtong, S., Athikomkulchai, S., & Chittasupho, C. (2020). Antifungal Activity and the Chemical and Physical Stability of Microemulsions Containing Citrus hystrix DC Leaf Oil. Natural Product Communications, 15(9), 1934578X20957755. doi: 10.1177/1934578X20957755
109. Rangsimawong, W., Wattanasri, P., Tonglairoum, P., Akkaramongkolporn, P., Rojanarata, T., Ngawhirunpat, T., & Opanasopit, P. (2018). Development of Microemulsions and Microemulgels for Enhancing Transdermal Delivery of Kaempferia parviflora Extract. AAPS PharmSciTech, 19(5), 2058-2067. doi: 10.1208/s12249-018-1003-6
110. Salimi, A., & Shirani, M. (2021). Antifungal Activity

of Topical Microemulsion Containing Ziziphus spina- christi L. for the Treatment of Fungal Vaginitis. 43-50.

111. Shao, H., Xi, N., & Zhang, Y. (2018). Microemulsion formulation of a new biopesticide to control the diamondback moth (Lepidoptera: Plutellidae). Scientific Reports, 8(1), 10565. doi: 10.1038/s41598-018-28626-0
112. Köksal Karayıldırım Ç, Üstündağ Okur N, Okur ME, Caglar EŞ, Nalbantsoy A, Alsakını KAMH, Karabay Yavasoglu NÜ (2024) Preparation, characterization, and toxicity evaluation of microemulsion formulation containing Prunetin for potential oral applications. Drug Chem Toxicol 47:235–242
113. Teja PK, Mithiya J, Kate AS, Bairwa K, Chauthe SK (2022) Herbal nanomedicines: recent advancements, challenges, opportunities and regulatory overview. Phytomedicine 96:153890
114. Leanpolchareanchai J, Teeranachaideekul V (2023) Topical microemulsions: skin irritation potential and anti-inflammatory effects of herbal substances. Pharmaceuticals 16:7
115. Parveen, R.; Akhtar, N.; Mahmood, T. Topical microemulsion containing Punica granatum extract: Its control over skin erythema and melanin in healthy Asian subjects. Poste¸py Dermatol. Alergol. 2014, 31, 351–355. [CrossRef] [PubMed]
116. Wani S, Rajput A, Pingale P (2023) Herbal nanoformulations: a magical remedy for management of fungal diseases. J Herb Med 42:100810
117. Pandey SS, Maulvi FA, Patel PS, Shukla MR, Shah KM, Gupta AR, et al. Cyclosporine laden tailored microemulsion-gel depot for effective treatment of psoriasis: in vitro and in vivo studies. Colloids and Surfaces. B, Biointerfaces 2020; 186:110681. https://doi.org/10.1016/j.colsurfb.2019.110681.