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Review Paper

Innovations in Antifungal Drug Delivery: The Role of Transferosomes

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ABSTRACT

Fungal infections, commonly referred to as mycosis, can affect humans in a variety of ways. As eukaryotic creatures, these viruses have the ability to enter their eukaryotic hosts and produce superficial, subcutaneous, or systemic infections. Fungal infections are usually cutaneous, but if the immune system is weakened, they can spread throughout the body and cause higher rates of morbidity and mortality. To treat these infections, antifungal drugs are thus necessary. There are a number of conventional formulations for the treatment of fungi, however their unregulated use has shown that fungal resistance has developed. Antifungal moieties have a lower oral absorption rate due to their lipophilia. Furthermore, they still struggle to get through the stratum corneum when they are included in nano-delivery systems like transferosomes, niosomes, and liposomes. Transferosomes are well-known vesicular carrier systems that may transport a range of medications over the skin's barriers. Due to their ultra-deformable qualities, which allow them to penetrate membranes and deliver medications to deeper areas, they gained notoriety. They offer a nice alternative for antifungal medication delivery because of their small size, reduced PDI, enhanced trapping, extended-release, and safety. Thus, transferosomes can be employed to alleviate barrier-related problems and enhance penetration and permeability. A better alternative to the present conventional delivery techniques is provided by this review, which also looks at their applicability to fungal illnesses and provides more explanation on their appropriateness.

INTRODUCTION

Infections, encompassing a wide range of illnesses caused by different microorganisms such as

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bacteria, viruses, fungi, and parasites, constitute a substantial worldwide health burden. These infectious agents take advantage of weaknesses in the host's immune system to cause a variety of clinical symptoms, ranging from minor ailments that go away on their own to serious diseases that can be fatal (Hill et al., 2024). Public health faces serious difficulties from the emergence and recurrence of infectious illnesses, which are prompted by components including globalisation, climate change, and antibiotic resistance. A multifaceted strategy is required for effective infection control methods, including vaccination campaigns, antimicrobial stewardship, better sanitation and hygiene practices, and the creation of innovative diagnostic and treatment instruments(Morse, 1995). From the above-mentioned various pathogens, fungal infections (FIs) are a major worldwide health concern, ranging from superficial dermatophytes to potentially fatal systemic mycoses(Lange et al., 2023). These diseases are becoming more common and more severe due to factors including climate change, rising antibiotic resistance, and the increase in immunocompromised people (Ibe & Otu, 2022; Richardson & Lass-Flörl, 2008). Fungi are very adaptive, using a variety of strategies to overcome host defences, including phenotypic flipping, capsule formation, and the synthesis of virulence agents like proteases and poisons. Due to the limits of traditional diagnostic techniques and the inevitably subtle clinical presentations, diagnosing fungal infections can be difficult. However, there are few effective antifungal treatments available, and new medication resistance makes treatment choices even more challenging(Martins-Santana et al., 2023). Therefore, to enhance patient outcomes and lessen the worldwide burden of these common pathogens, further research is essential in the pathophysiology, diagnosis, and treatment of fungal infections. Fungi are parasitic microbes that can cause systemic infections of several internal organs and damage the skin and mucous membranes (Kim, 2016). Unquestionably, the number of fungal infections has grown recently, and they are considered a significant emerging ailment that poses a threat to millions of lives worldwide (Kainz et al., 2020). It has been estimated that between 20% and 25% of people are affected by FIs, as previously reported in the literature (Aditya K. et al., 2005). Fungi are ubiquitous within various environments, including domestic residences, healthcare facilities, hospitality establishments, recreational areas, horticultural settings, and as commensals on human skin and mucous membranes. These newly discovered infections are a significant contributor to both morbidity and death(Gupte, 2015). Both primary and opportunistic infections are possible classifications for fungi of medical importance. While opportunistic infection happens in immunocompromised individuals, primary infection happens in healthy individuals who have not been exposed to endemic fungi (Dixon et al., 1996; Lehrnbecher et al., 2010). Aspergillus spp., Fusarium spp., and Candida spp. represent the most frequently isolated fungal organisms(Kainz et al., 2020). The predominant manifestations of fungal disease involve superficial infections of the skin and nails, primarily attributed to dermatophytes, clinically manifesting as tinea pedis (athlete's foot), tinea capitis (ringworm of the scalp), and onychomycosis (nail infections) (Havlickova et al., 2008; Thomas et al., 2010). Infections caused by fungi are the most common and are growing at a startling rate, making it extremely difficult for medical professionals to detect and treat them. The majority of fungi are common and can reproduce efficiently without the aid of substrates in their natural environments.

Since the medication is applied directly to the affected region, topical therapy of fungal infections is typically chosen over systemic

treatment due to its lower adverse effects and increased patient compliance (Pandit et al., 2014). However, the stratum corneum, the outermost layer of the skin, is the main obstacle to drug penetration. For antifungal medications, a drug delivery method that can get beyond the stratum corneum's barrier qualities must be created (El Zaafarany et al., 2010a; Pandit et al., 2014).

In its widest definition, a transfersome is a difficult aggregation that is extremely adaptive and sensitive to stress. Its ideal shape is a greatly flexible vesicle with a complex lipid bilayer enclosing an aqueous core. The vesicle is self-regulating and self-optimizing due to the interdependence of the bilayer's structure and local composition. For non-invasive targeted drug delivery and continuous release of therapeutic drugs, this allows the Transfersome to effectively traverse a variety of transport obstacles and thereafter function as a drug carrier (Modi & Bharadia, 2012). However, certain species of human pathogens are extraneous and can cause systemic, subcutaneous, or superficial infections. Most fungi that cause systemic (or deep-seated) infections enter the body through the lung or by wound or inhalation. Common occupants of the epidermis and gastrointestinal tract, other infections, such as Candida albicans, can multiply and penetrate the systemic circulation under specific conditions, such as when they enter the human body through medical devices like catheters. Polyenes, Azoles, and Echinocandins are the only three kinds of compounds that are currently useful in treating fungal infections. Table 1 goes into summarising detail about them. Although polyenes are poisonous and less stable, they are nonetheless utilised as first-line drugs (Day et al., 2013a). Although they are less harmful, azoles do not work against many fungi. Echinocandins, on the other hand, are utilised as azole substitutes and are safer (Perlin, 2007).

This review focuses on fungal infections that pose a significant threat to human health, often resulting in mortality. We provide a comprehensive overview of various fungal infection types and summarize current therapeutic strategies, including conceptual approaches to treatment utilizing diverse pharmacological agents. Furthermore, we explore the mechanisms of drug delivery to the site of infection. Finally, we conclude this review by outlining potential avenues for future research in this field.

2. Types of fungal infections

A number of fungal diseases can develop and recur often, including aspergillosis, cryptococcosis, candidiasis, mucormycosis [zygomycosis], and pneumocystosis. However, candidemia is one of the main causes of systemic infections, with a mortality rate of over 30%, and Aspergillus can infect over 45% of the susceptible hosts. Diabetes, the most common illness worldwide, is impacted by zygomycosis, especially in India. The mortality rate from invasive fungal infections was 67%. (Chakrabarti et al., 2009; Maschmeyer et al., 2007). Table 2 below lists the most common fungal diseases that humans get.

2.1. Superficial fungal infections

Many fungi that may infiltrate different parts of the human body are the source of superficial fungal infections. Dermatophytes, which infect keratinised epithelium, hair follicles, and nail apparatus; Candida sp., which requires a warm, humid environment; Malassezia sp., which needs lipids and a humid milieu to flourish; Trichosporon sp., and Hortae sp. are some of these illnesses. Dermatophytes infect keratinised, nonviable cutaneous structures like hair, nails, and stratum corneum (Havlickova et al., n.d.; Seebacher et al., 2008). Dermatophytosis of the nail apparatus is known as onchomycosis, trichomycosis is the dermatophytosis of hair and hair follicles, and epidermomycosis is an infection of the epidermis. Trichophyton sp., Microsporum

sp., and Epidermophyton sp. are the three genera of dermatophytes. Both onchomycosis and epidermal dermatophytosis are most frequently caused by Trichophyton rubrum (Ameen, 2010).

Infections with dermatophytes can be obtained via soil, transferred from animals to people, or spread from person to person by fomites. Atopic diathesis, including cell-mediated immune insufficiency for T rubrum, extended immunosuppression with topical glucocorticoid usage, and systemic immunocompromised states, are risk factors for complex dermatophyte infections (Ameen, 2010).

2.1.1. Tinea Pedis

Infections caused by dermatophytes are categorised by body parts. Tinea is a sign of a fungal infection. The dermatophyte infection of the foot, known as athlete's foot, is tinea pedis, as seen in Fig. 1. Sweating and warmth encourage the development of fungi. When making a differential diagnosis for children with foot dermatitis, tinea should be taken into account (Mcbride & Cohen, n.d.). The flooring of locker rooms are ideal for the development of fungi. Using public restrooms makes it perfect for repeated exposure. Males are more impacted than females, and the most prevalent age span impacted is late infancy to early adulthood. The majority of tinea pedis infections occur on the soles or in toe webs, however it can also manifest as the traditional ringworm pattern. It frequently involves the web between the fourth and fifth numbers. The web may become white, macerated, and wet, or it may become dry, scaly, and fractured. When shoes and socks are taken off, the most common complaint is itching (Kates et al., 1990). Since the macerated portion of the infection results from the interaction between bacteria and fungus, the severity of this interdigital toe web infection is determined by the overgrowth of the resident bacterial population. By producing antibiotics, dermatophytes cause harm to the stratum corneum and affect the selection of bacteria that are more resistant to antibiotics, including group B streptococcus and methicillin-resistant Staphylococcus aureus. Clinical diagnosis is made. On the other hand, dermatophyte isolation on culture and hyphae demonstration on direct microscopy are likewise accessible. The condition known as "two feet, one hand" is characterised by tinea in one palm and dermatophyte infection in both feet. Additionally, there may be nail infections on the hands and feet. T rubrum is the causal organism in the majority of cases, which mostly affect men (Daniel et al., 1997). The most recent family of antifungal drugs cures dermatophyte infections more quickly and with greater cure rates. For four weeks, including one week after the lesions are cleared, topical antifungal medications should be used twice daily in the affected region. Clotrimazole, miconazole, and ketoconazole are among the topical medications that belong to the imidazole class. Additionally, terbinafine 1% cream can be used. Systemic antifungal medications, such as terbinafine 250 mg pill daily for 2 weeks, itraconazole 200 mg twice daily for 1 week, or fluconazole 150 mg once weekly for 2–6 weeks, should be used if the infection spreads or does not improve with topical therapies. Wearing larger shoes and using a tiny piece of lamb's wool to increase the web area will stop recurrence. Powders should be put to the feet rather than the shoes since they will absorb moisture.

2.1.2. Tinea Capitis:

Tinea of the scalp, also known as tinea capitis, can present in a variety of ways and is most common in prepubertal children aged 3 to 7 (Hubbard, n.d.). The most likely dermatophyte species to cause this illness are anthropophilic species, which are present in people. Tinea capitis, as seen in Figure 1, is especially prevalent in impoverished and congested locations. Contact with an infected person or pet is the source of the infection. Direct contact is not required for transmission since

spores are released into the air near the patient. Direct touch or wearing infected garments can spread scalp tinea. Fungal infection rates are more closely associated with large family sizes, crowded living conditions, and poor socioeconomic position. For months, infectious particles expelled by an infected individual can remain alive. Animals, infected people, dropped hairs, fomites (clothes, bedding, hairbrushes, combs, and caps), and furniture are common ways for the disease to spread. Untreated asymptomatic scalp infections in adults and school-age children are significant risk factors for reinfection and disease transfer. The carrier remains asymptomatic for an indeterminate amount of time (Frieden, 1987). Small-spored ectothrix, large-spored ectothrix, and large-spored endothrix are the three types of hair invasion patterns. There are differences in the inflammatory response to infection. The term "kerion" refers to a severe inflammatory reaction that resolves with scarring and minor hair loss. It is characterised by a swampy, indurated, tumorlike mass that discharges pus. Additionally, cervical or occipital lymphadenopathy may be observed; in the absence of lymphadenopathy, the diagnosis of tinea capitis should be questioned. Psoriasis and seborrhoeic dermatitis are frequently mistaken for scalp tinea. A common misdiagnosis for tinea is tinea amiantacea, a kind of seborrhoeic dermatitis that affects youngsters. The localised 2- to 8-cm area of big, brown, polygonal scales known as tinea amiantacea sticks to the scalp and mats the hair. Without much irritation, the matted scale that is affixed to the hair grows out (Frieden, 1987; Hubbard, n.d.).

2.1.3. Tinea Versicolor

The widespread fungal skin illness known as tinea versicolour (**Figure 1**) is brought on by the dimorphic lipophilic yeasts Pityrosporum orbiculare and Pityrosporum ovale. Malassezia furfur was the old name for both organisms (A. K. Gupta et al., 2003). The organism, which is a component of the natural skin flora, is most prevalent in areas with high sebaceous activity. It feeds on triglycerides and free fatty acids in the stratum corneum and hair follicles. Yeast can change from the budding yeast form to its mycelial form, which results in tinea versicolour. Predisposing factors include adrenalectomy, Cushing's disease, pregnancy, malnutrition, burns, corticosteroid therapy, immunosuppression, decreased cellular immunity, and oral contraceptives. Although the illness can strike at any age, it is more prevalent in adolescents and young adults (Nanda et al., 1988; Wyre, 1981). Multiple tiny, round macules of different hues (white, pink, or brown) that grow quickly are the first signs of a lesion. A variety of clinical manifestations are produced by tinea versicolour infections, such as: (1) hyperaemic inflammatory response-induced red to fawn-colored macules, patches, or follicular papules; (2) hypopigmented lesions; and (3) tan to dark brown macules and patches. Hypopigmentation results from injury to melanocytes. Pityrosporum sp. produces dicarboxylic acids that can inhibit the dopa tyrosinase process and have a deleterious impact on melanocytes. Melanocytes and the surrounding keratinocytes experience a decrease in the quantity, size, and aggregation of melanosomes. As untreated skin tans, white hypopigmentation becomes more noticeable (GALADARI et al., 1992; Nazzaro Porro & Passi, 1978). Although the illness can extend to the upper arms, neck, and belly, it most frequently affects the upper trunk. Children frequently have facial lesions, particularly on the forehead. Aside from skin colouration, the eruption is often asymptomatic, however it may itch if it is inflammatory. This condition can be distinguished from vitiligo, pityriasis rosea, seborrhoeic dermatitis, pityriasis alba, and secondary syphilis. The scale may be examined under a microscope using potassium

hydroxide and light scraping to make the diagnosis. It should display a large number of hyphae that break into short, rod-shaped fragments mixed with spherical spores in clusters that resemble spaghetti and meatballs (Nazzaro Porro & Passi, 1978).

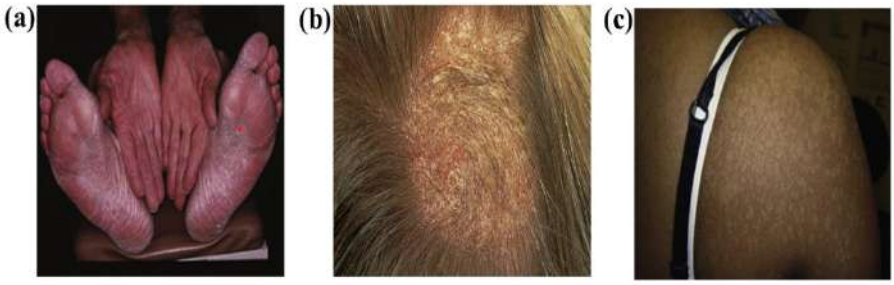

Figure 1: Superficial fungal infections (a) tinea pedia, reproduced with the permission (Kaushik et al., 2015). 2015 Elsevier. (b) tinea capitis, reproduced with the permission(Hay, 2013). 2013 Elsevier. (c) tinea versicolor, reproduced with the permission (Kaushik et al., 2015). 2015 Elsevier

2.2. Subcutaneous fungal infections

In immunocompetent hosts, subcutaneous mycoses are fungal infections that mostly affect the dermis and subcutaneous tissue and seldom spread (Patel et al., 2011). These infections, which are most frequently observed in tropical regions, typically arise from the implantation of ubiquitous organisms into the skin through local trauma. Immunocompromised individuals are more susceptible to these infections, as is the case with other mycoses (La Hoz & Baddley, 2012). Sporotrichosis, chronic mucocutaneous candidiasis, and chromoblastomycosis are the three primary subcutaneous mycoses.

2.2.1. Chromoblastomycosis

The most common subcutaneous infection in the tropics is chromoblastomycosis (CB), which is caused by pigmented fungus inoculating the skin traumatising immunocompetent hosts. Fungi belonging to the genera Fonsecaea (tropical woods), Cladophialophora (dry regions), and Philalophora are the main culprits (Patel et al., 2011). The condition is more frequently seen in lower-leg agriculturists, which probably explains why males from lower socioeconomic backgrounds are more likely to have it. A papule or nodule that is asymptomatic and gradually grows over years into a localised verrucous plaque that enlarges and leaves behind a central sclerotic or keloidal scar is the classic first sign of chromoblastomycosis. The surface of the lesion may contain distinctive black spots, which are the host's effort to remove fungal components transepidermally. Although satellite lesions from autoinoculation and lymphatic dissemination have been seen, the illness usually stays localised. Bacterial superinfection, ulceration, secondary lymphoedema, and, in rare cases, the emergence of squamous-cell cancer are examples of secondary consequences. Extension into the skeletal muscle and bone underneath is a concern in an immunocompromised state. Identification of thick-walled, multiseptate, brown, sclerotic cells known as muriform cells, Medlar bodies, or copper pennies is necessary for the diagnosis of chromoblastomycosis. Tissue biopsy specimens or a direct microscopic analysis of a scrape of black spots from the nodule's surface using 10% potassium hydroxide can both reveal these pathognomonic characteristics. Although tissue culture can be used to identify the causal fungus species, the results are not always favourable(La Hoz & Baddley, 2012; Patel et al., 2011).

2.2.2. Sporotrichosis

The dimorphic fungus Sporothrix schenckii is the cause of sporotrichosis, which is presently found

all over the world, but particularly in tropical and subtropical regions. The most common method of infection is traumatic inoculation of fungus-contaminated soil, plants, and organic materials. Mycosis has historically been linked to a number of recreational and professional pursuits, including farming, mining, timber exploitation, and floriculture. Small outbreaks or sporadic occurrences of zoonotic transmission have been reported. Currently, a new risk group for contracting sporotrichosis is thought to include veterinarians, technicians, carers, and owners of cats infected with the disease (Barros et al., 2011). The epidermis, subcutaneous cellular tissue, and nearby lymphatic arteries are often the only areas where the lesions are seen. This fungus can eventually spread to other organs, or in rare cases, a systemic illness may result from conidia inhalation. The many clinical manifestations of sporotrichosis are influenced by a number of parameters, including the inoculum load, the host's immunological condition, the virulence of the injected strain, and the depth of traumatic injection. Although culture is the gold standard for detecting sporotrichosis, molecular, histological, and serological methods have lately been used as supplemental diagnostic techniques (Mahajan, 2014).

2.2.3. Chronic mucocutaneous candidiasis

A group of diseases known as chronic mucocutaneous candidiasis are defined by recurring or persistent infections of the skin, nails, and mucous membranes caused by organisms belonging to the genus Candida; Candida albicans is the causative agent in almost all of these instances. The illness often manifests within the first three years of life, however it can manifest at any age. The number of afflicted males and females is almost equal. The patient usually develops thrush, or chronic or recurrent oral candidiasis, which may be followed by or accompany perianal and perineal cutaneous candidiasis. Subsequently, the scalp, torso, and extremities then develop lesions(Qian et al., 2024). The first sign of nail involvement may be paronychia. Although patients may have widespread Candida albicans infections of the buccal, cutaneous, and ungual regions, there is almost little risk of sepsis, pneumonia, or Candida infections of the parenchymal organs. This is an intriguing clinical feature of the illness(Kirkpatrick, 1989).

2.3. Systemic fungal infections

Systemic fungal infections can spread to many other organs and typically start in the lungs (aspergillosis and other mould infections from inhalation) or endogenous flora (candidaemia from infected lines or leaking from the gastrointestinal tract). High death rates and medical crises are associated with systemic fungal infections, particularly if adequate management is postponed. Antifungal medication only works partially in immunocompromised hosts; to increase results, immunotherapeutic adjuvant medicines such as colony-stimulating agents are required. Azole resistance in Aspergillus and Candida species, followed by echinocandin and multidrug resistance in some Candida species, particularly Aspergillus and Candida glabrata, is one of the biggest obstacles to therapeutic success in the increasing issue of antifungal resistance (Perlin et al., 2017).

2.3.1. Histoplasmosis

Although histoplasmosis is found nationwide, it is most prevalent in the Mississippi and Ohio valleys, where exposure rates can reach over 80%. Although the majority of instances are asymptomatic, severe exposure can cause acute respiratory symptoms and progressive pulmonary illness that resembles TB, especially in those who already have lung disease. Disseminated sickness happens at the very end of life and in immunocompromised people, especially those with AIDS. Fever, weight loss,

hepatosplenomegaly, and widespread lung and frequently gastrointestinal involvement are the hallmarks of this condition(Rautemaa-Richardson & Richardson, 2017).

2.3.2. Penicilliosis

Penicillium marneffei is the causative agent of penicilliosis, which is endemic in southern China and Southeast Asia. It is the third most prevalent opportunistic illness among AIDS patients in northern Thailand. Similar to histoplasmosis, but frequently accompanied by skin lesions, these patients have a disseminated illness (Rautemaa-Richardson & Richardson, 2017).

2.3.3. Cryptococcosis

The infectious illness known as cryptococcosis is brought on by pathogenic encapsulated yeasts belonging to the genus Cryptococcus. Although they are present all around the planet, the causal species' distribution varies. Even in environments where C. gattii is present, infection is often caused by C. neoformans var. neoformans. The main risk factor for Cryptococcus gattii is exposure to the environment; it primarily affects those who are not compromised. Immunocompromised individuals, particularly those with AIDS, are at risk for the majority of infections. It is thought that inhaling desiccated spores causes infection. It's possible that the prostate harbours infections. There is also a chance of environmental reinfection (Noguchi et al., 2019). Thirty percent of generally healthy people have a pulmonary infection with no symptoms; others have fever, weight loss, chest discomfort, and productive cough. The most frequent clinical manifestation is meningitis, which develops slowly. Endophthalmitis and osteomyelitis may develop, and it may be linked to cutaneous lesions in widespread illness. A significant increase in intracranial pressure frequently results in cranial nerve palsies and, in the absence of therapy, blindness(Chayakulkeeree & Perfect, n.d.; Rautemaa-Richardson & Richardson, 2017).

2.3.4. Blastomycosis

In healthy people, Blastomyces dermatitidis or B. gilchristii causes a lung illness called blastomycosis. However, it frequently spreads to other organs, especially the skin and bones. It may be found in sections of Africa, Central and South America, and the midwestern and southeast regions of North America (Rautemaa-Richardson & Richardson, 2017).

2.3.5 Invasive aspergillosis

Infections brought on by moulds of the genus Aspergillus, which are present all over the world, are referred to as "aspergillosis." They might be anything from minor infections to serious systemic diseases. An allergic response to spores breathed can also cause disease. There are at least 350 known species. Aspergillus species can be found in soil, air, plants, and decaying organic waste. They can also be found in dust and on food in homes and hospitals, particularly in ceiling voids, foods, plants, and textiles. They can also be discovered in conjunction with construction or demolition activities, or in areas with inadequate ventilation (Perlin et al., 2017).

2.3.6. Invasive candidiasis/ candidaemia

A serious bloodstream infection known as invasive candidiasis, or candidemia, is brought on by Candida species, mostly Candida albicans, however non-albicans species such as Candida glabrata, Candida parapsilosis, and Candida tropicalis are becoming more prevalent (Nazzaro Porro & Passi, 1978).Patients with impaired immune systems, such as those receiving chemotherapy, organ transplants, or extended intensive care unit stays with central venous catheters, are usually at risk for contracting this illness(Logan et al., 2020). In addition to having a high rate of morbidity and death, the illness can cause extensive involvement of other organs, including the kidney, liver, and spleen. The diagnosis frequently uses sophisticated molecular testing and blood cultures. Treatment with

antifungal drugs, such as azoles (like fluconazole) or echinocandins (like caspofungin), must be started as soon as possible. Effective management necessitates removing or replacing contaminated catheters as well as treating underlying problems. Delays in treatment dramatically decrease results, despite advancements in antifungal medication, highlighting the need of early detection(BEN BRAHIM et al., 2023; Pappas et al., 2018).

2.3.7 Zygomycosis

Moulds of the Mucorales order are the source of zygomycosis, an uncommon but dangerous fungal illness that is now more frequently known as mucormycosis. These fungus, which include species including Rhizopus, Mucor, and Lichtheimia, are found in soil, decomposing organic debris, and the air. Immunocompromised people, such as those with untreated diabetes, haematologic malignancies, or those on long-term corticosteroid therapy, are the main victims of mucormycosis(Skiada et al., 2018). Rhinocerebral, pulmonary, gastrointestinal, and cutaneous infections are among its many manifestations. Rapid progression and angioinvasion, which results in tissue necrosis, are the disease's defining characteristics. Prompt antifungal treatment, frequently with liposomal amphotericin B, and rigorous surgical debridement of afflicted tissues are part of the treatment. The need of early intervention is highlighted by the high death rate that can arise from delays in diagnosis and treatment(Cornely et al., 2019).

Table 1: Clinical classification of fungal infections in humans.

Type of infection	Disease	Fungus responsible	Clinical manifestations	References
Superficial fungal infections	Tinea versicolor (chest, back, neck and arms)	Malassezia furfur	Hypo- or hyperpigmentation; white skin with reddish, somewhat scaly blemishes.	(Kallini et al., 2014; Kumar Rai & Wankhade, 2009)
	Tinea pedis (feet)	Trichophyton rubrum, T. mentagrophytes var. interdigitale T. rubrum, Candida spp., T. mentagrophytes var. Mentagrophytes, and some molds	the possibility of scaling and irritation that spreads to the sole. The nails are swollen, discoloured, and fractured, and the plate of the nail has detached from the root.	(Ilkit & Durdu, 2015)
	Tinea capitis (scalp)	T. tonsurans, Microsporum audouinii	Scaling and hair loss on the scalp, often with crusting, oozing, and itching.	(Seebacher et al., 2007)
Subcutaneous fungal infections	Chromoblastomycosis	Dematiaceae family	skin lesions that are crusted and elevated.	(Queiroz-Telles et al., 2009)
	Sporotrichosis	Sporothrix schenckii	A skin or subcutaneous tissue lesion that can spread through the lymphatic system and result in ulcers, reddish to yellowish papules, and new lesions on the hand, arm, or finger.	(Barros et al., 2011; Mahajan, 2014)

	Chronic mucocutaneous candidiasis	Candida spp. [mostly C. albicans]	White fissured lesions; granulomatous, hyperkeratotic, and vegetating lesions; a disorder that is autosomal recessive and linked to endocrine issues.	(Qian et al., 2024)
Systemic fungal infections	Invasive candidiasis/ candidaemia	C. albicans and other Candida spp	A CT scan can reveal minute radiolucent lesions in the liver or spleen of a patient with chronic invasive candidiasis. Prolonged-resistant fever, sometimes accompanied by hepatic and splenic enlargement, stomach pain, and weight loss.	(Logan et al., 2020)
	Cryptococcosis	Cryptococcus neoformans	Although haematogenous spread can result in extensive skin lesions, meningitis is the most common clinical symptom.	(Maziarz & Perfect, 2016; Noguchi et al., 2019)
	Invasive aspergillosis	Aspergillus spp.	Prolonged fever: CT scan shows halo and/or air crescent symptoms; histologically, non-pigmented, septate hyphae with dichotomous branching are seen. On radiography, one or more lesions may be seen.	(Dagenais & Keller, 2009)
	Zygomycosis	Rhizopus spp. Absidia spp. Mucor spp.	In addition to disseminated mucormycosis, which primarily affects the brain and may cause lesions that spread to the spleen, heart, and other organs, rhinocerebral, pulmonary, gastrointestinal, or cutaneous areas can all develop mucormycosis.	(Mantadakis & Samonis, 2009; Natesan, 2020)
	Penicilliosis	Penicillium marneffei	Arthritis, an enlarged spleen, skin lesions, subcutaneous abscesses, bone lesions, lymphadenitis, and lung, liver, or colon lesions are all indicators of multiple organ involvement.	(Sirisanthana & Supparatpinyo, 1998)
	Histoplasmosis	Histoplasma capsulatum	In HIV-positive people, pulmonary, extrapulmonary, or disseminated infection can cause mouth ulcers, pancytopenia, hepatosplenomegaly, and other skin signs.	(Azar & Hage, 2017; Baker et al., 2020)

	Blastomycosis	Blastomyces dermatitidis	The ulcerative or verrucous cutaneous lesions that define the chronic progressive form might damage the skin, genitourinary tract, bone, or central nervous system.	(Hussaini et al., 2018; McBride et al., 2017)

3. Classification of antifungal drugs:

The range of molecular targets that may be utilised in drug development is limited since the fungi mentioned above are classified as eukaryotes. There are now just three types of molecules available for treating invasive mycoses. Among these compounds are echinocandins, polyenes, and azoles. Echinocandins act on the formation of cell walls, polyenes target the ergosterol itself, and azoles target the synthesis of ergosterol (Robbins et al., 2016a). The efficacy of these drugs is compromised by the host, toxicity, fungistatic action, or the emergence of drug resistance in infectious populations. According to their clinical use, antifungal medications are classified into four categories: polyenes, pyrimidines, azoles, and echinocandins, as shown in Table 2. New generations of antifungal medications with improved therapeutic properties are available thanks to significant improvements in their research. The emergence of new generations of antifungal medications with better therapeutic results for these vulnerable patient groups represents significant advances in the discovery of new antifungal medications. Therefore, first-generation azole medications like fluconazole and itraconazole were introduced in the 1990s after a wait of more than 20 years (Nett & Andes, 2016). The 2000s saw the introduction of second-generation azole medications including voriconazole, posaconazole, and isavuconazole as well as echinocandins (caspofungin, anidulafungin, and micafungin). The functional fungal analogue of cholesterol, ergosterol, is the target of the majority of antifungal compounds. Ergosterol production is an essential part of the fungal cell wall. Since all therapies have a common target, which makes cross-resistance to those medications prevalent, the decreased incidence of fungus-specific targets is essential. In the medical world, resistance to widely used antifungals is becoming a bigger problem (Shapiro et al., 2011). The potent but hazardous family of chemicals with antifungal properties are called polyenes. Nephrotoxicity has been documented as a frequent side effect, and they are linked to high selectivity (Ostrosky-Zeichner et al., 2010). On the other hand, pyrimidine molecule treatment is employed in conjunction with polyenes since it has been found to have antifungal resistance (Day et al., 2013b). In contrast, the safety profile of azoles is superior. Due of its immobile nature, fungi are under a lot of directed pressure to evolve resistance. These medications have less of an impact on Candida species such as C. krusei and C.glabrata (Robbins et al., 2016b). Although they are quite effective against Aspergillus and Candida, echinocandins have a superior safety record and are unable to treat Cryptococcus infections. Because of their increased azole resistance, they are regarded as a significant alternative to treat candidiasis (Perlin, 2007).

3.2 Clinically used classes of antifungal medications.

Polyenes: Amphotericin B, a broad-spectrum polyene antibiotic, was the first standard of care for a variety of invasive fungal infections. Ergosterol, the main sterol in fungal membranes, is firmly bound by amphotericin B. Intracellular components can leak out of membrane holes created by aggregates of amphotericin B–ergosterol complexes (Gruszecki et al., 2003).

Amphotericin B's selective toxicity is explained by its differing binding affinities for ergosterol and cholesterol, the sterol found in mammalian membranes. However, nephrotoxicity is a frequent side effect of therapeutic use of amphotericin B, and it can also harm mammalian cells (Fanos & Cataldi, 2000). The frequency of renal toxicity from amphotericin B was significantly decreased with the introduction of lipid-complexed formulations. Nowadays, two lipid products—a lipid complex and a liposomal formulation—are often employed to treat a variety of serious mycoses. Only two new polyenes, modifications of existing polyenes, and innovative formulations of polyenes fit the requirements to be included in this review, despite the fact that many more have been reported. Experimental models of aspergillosis and candidiasis have demonstrated the effectiveness of a cochleate formulation of amphotericin B (Delmas et al., 2002; Santangelo et al., 2000; Zarif et al., 2000). The amphotericin B molecules are trapped in a sizable, stable, spirally rolled lipid bilayer by this formulation. Amphotericin B's oral bioavailability is promised by the formulation; nevertheless, the only pharmacokinetic investigation conducted to far has used intravenous administration in mice (Segarra et al., 2002). The cochleate formulation is a product of BioDelivery Sciences International, which presently lists the product as being in preclinical research. However, the current development status is unknown. Numerous preclinical and clinical investigations have been conducted on a liposomal formulation of tetraene nystatin (Ellison, 2002). The outcomes of Phase III clinical studies for the treatment of fever in cryptococcal meningitis and neutropenia, however, have not been thoroughly documented or published in the peer-reviewed literature. Therefore, it is uncertain how liposomal nystatin develops.

Azoles. In terms of the number of distinct medicines that have been put into clinical use, the imidazole and triazole antifungal class has had the most success. However, due to issues with toxicity or absorption that restrict their potential as systemic treatments, the majority of antifungal imidazoles are solely designed for topical use. Fluconazole, itraconazole, posaconazole, and voriconazole are the triazoles that have been approved for clinical use in invasive fungal diseases. As demonstrated by their development over the previous 30 years, voriconazole and posaconazole represent particular advancements in our understanding of the structure–activity correlations for antifungal azoles. In systemically active azoles, a triazole-based pharmacophore has taken the place of the previous imidazole pharmacophore because the triazole group slows the drugs' metabolism in vivo and improves specificity for fungal cytochrome P450 (Erg11) targets (Ellison, 2002). The additional methyl group at carbon atom number three in a fluconazole-based structural type increases hydrophobic interactions at the Erg11 active site and broadens the antifungal range (Fukuoka et al., 2003). Triazole drugs now often have a 2,4-difluorophenyl substituent at carbon atom number two instead of a dichlorophenyl. Mouse models of fungal illness have shown that replacing the 1,3-dioxolane moiety in ketoconazole and itraconazole with a furan ring, as in posaconazole, changes and increases action (Keating, 2005). These optimised structural characteristics are advantageous for triazole drugs in the development pipeline. In animal models of infections brought on by Aspergillus, Candida, Cryptococcus, and Scedosporium species, the oral active ingredient has demonstrated effectiveness (Sorbera et al., 2003). It may no longer be being developed for invasive fungal illness, nevertheless, based on its most recent placement in a Phase II study for vulvovaginal candidiasis. There doesn't appear to

be an intravenous version of albaconazole. Eisai made the first discovery of Ravuconazole (BMS-207147), which Bristol-Myers Squibb developed significantly as an oral broad-spectrum triazole for invasive mycoses. It does not appear to be actively being developed at this time, and no intravenous formulation has been created. The oral active, water-soluble prodrug BAL-8557, which may be administered intravenously, is a development of the ravuconazole isomer isavuconazole (BAL-4815) (Odds, 2006). Only the compounds on the above list fit the description of the antifungal pipeline used in this article, which is prospective candidates that are approaching or already in clinical development. Many novel antifungal triazole molecules are revealed in original research publications and patents. It is too soon to tell if any of the triazoles listed will actually outperform currently approved triazoles. By enhancing the drug-drug interaction profile or broadening the spectrum of activity to include uncommon but challenging-to-treat invasive mycoses (infections brought on by Fusarium spp., Scedosporium spp., or the Zygomycota), new triazoles may be advantageous. Furthermore, novel triazoles may have a more favourable adverse effect profile and/or a pharmacokinetic profile that would significantly lower the frequency of dose. However, due to a lack of clinical evidence, none of the triazoles currently under development have demonstrated these benefits.

Sordarins. It was discovered in the early 1970s that a family of natural semi-synthetic compounds called sordarins have antifungal properties (Hauser & Sigg, 1971). The preclinical development of many innovative sordarin compounds by Glaxo-Wellcome and Merck in the 1990s sparked a lot of interest in them (Odds, 2001). Elongation factor 2 in protein biosynthesis is a new target for antifungal medicines, and the drugs were shown to inhibit it (Domínguez & Martín, 1998). No clear candidate for clinical development has yet to surface, and since 2002, the frequency of publications on sordarins has significantly decreased. However, several compounds based on the sordarin pharmacophore have demonstrated therapeutic effectiveness in a variety of animal models of fungal illness (Hanadate et al., 2009; Kamai et al., 2005). Sankyo is the most recent business to express interest in sordarin antifungal medicines; in a variety of experimental models of candidiasis, sordarin R-135853 has demonstrated in vivo effectiveness . Excellent antifungal action against Candida albicans has been demonstrated by FR290581, a sordarin derivative that is currently being developed (Hanadate et al., 2009).

Echinocandins. Researchers are presently doing Phase III and Phase IV clinical studies on the three echinocandins already on the market—caspofungin, anidulafungin, and micafungin—as well as basic in vivo and in vitro modelling because the echinocandin family is still relatively young. Aminocandin (IP960/HMR3270) is the lone contender in early preclinical research, and the development of new drugs in this class is sluggish. This drug has demonstrated excellent action against filamentous fungus and Candida spp. both in vitro and in vivo (Ghannoum et al., 2007; Warn et al., 2005, 2010).

Table 2: clinically used classes of antifungal medications.

Major classes under clinical use	Mechanism of Action	References
Polyenes (Nystatin, AmB, and pimaricin)	• These molecules caused cell death by intercalating membrane-containing ergosterol and creating membrane-spanning channels that allowed cell components to escape.	(Anderson et al., 2014; Ostrosky-Zeichner et al., 2010)

	• Polyenes act more like a "ergosterol-sponge," generating large extramembranous aggregates that deplete the plasma membrane's vital membrane-lipid ergosterol.	
Pyrimidines (5-Fluorouracil, Cytosine Arabinoside, 5-Azacytidine, Gemcitabine)	• Fungal-specific cytosine deaminases quickly deaminate pyrimidines (flucytosine) in the cytosol to yield 5-fluorouracil. • 5-fluorouracil is a potent antimetabolite that inhibits DNA synthesis and encourages RNA miscoding.	(Loyse et al., 2013)
Azoles Imidazoles (Clotrimazole, Econazole, Ketoconazole, Miconazole, Tioconazole), Triazoles Fluconazole, Itraconazole, Posaconazole, Voriconazole	• The primary target of azoles is the heme protein, which co-catalyzes the cytochrome P-450-dependent 14 α α-demethylation of lanosterol [51]. When 14 α-demethylase is inhibited, ergosterol is reduced and sterol precursors, including 14-methylated sterols, build up. As a result, a plasma membrane with a modified structure and function is formed. • By inhibiting the cytochrome P-450-dependent 14 α-sterol demethylase, modern triazole medications like fluconazole, itraconazole, and voriconazole (a triazole in development) have antifungal effects.	(Warrilow et al., 2010)
Echinocandins (Caspofungin, Micafungin and Anidulafungin)	• These cyclic hexapeptides disrupt the enzyme [1,3]-β-D-glucan synthase, which is necessary for cell wall production. • The cell wall breaks down due to severe cell wall stress caused by the inhibition of [1,3]-β-D-glucan synthesis.	(Perlin, 2015)

3.1. Need for delivery systems for delivery of antifungal agents

Many antifungal drugs are lipophilic, which results in poor oral bioavailability, decreased water solubility, and few formulation options (Lewis, 2011). Lipophilia and low aqueous solubility are characteristics of several commonly used azole antifungal drugs, such as clotrimazole, miconazole, econazole, oxiconazole, tioconazole, and sertaconazole (Groll et al., 2003; A. K. Gupta & Cooper, 2008; Zhang et al., 2010). The toxicity and drug-drug interactions of systemic antifungal medicines are significant barriers that restrict their therapeutic effectiveness (Harbarth et al., 2001). Nephrotoxicity and infusion-related events were among the dose-limited toxicities brought on by AmB therapy. Furthermore, AmB makes several other drugs, such as cyclosporine and aminoglycosides, more nephrotoxic (Harbarth et al., 2001). Many common antifungal medicine dosage forms, such pills, lotions, IV infusions, and so forth, were available, but they didn't seem to be enough to get beyond these limitations. The development of novel pharmaceutical delivery systems is essential to resolving the problems. Several limitations may be addressed and the effectiveness of prescription drugs can be increased using rationally designed drug delivery systems. One of the lipid-based forms of the drug is the AmB lipid complex; colloidal dispersion of AmB and liposomal AmB both considerably decreased AmB nephrotoxicity while maintaining broad-spectrum antifungal activity (Arikan & Rex, 2001). Novel drug delivery methods that improve medication safety while preserving or boosting efficacy were developed as a result of these

encouraging findings. With the potential to lessen unwanted drug side effects while preserving or improving therapeutic effectiveness, NPs have become a unique and intriguing platform among the many innovative delivery methods being researched in business and academia (Zazo et al., 2016; Zhang et al., 2010). Many of the negative pharmacological traits may be addressed by NP because of its versatility, multifunctionality, and range of attributes. Moreover, NPs could enhance the skin's ability to absorb medications, which would help eradicate more serious fungal infections (Mbah et al., 2014). These NPs' extended blood residence length, enhanced therapeutic efficacy, prolonged drug release, reduced off-target side effects, and targeted tissue are additional desirable characteristics (Chang et al., 2015; Soliman, 2017). Transferosomes, an ultra-deformable liposomal vesicle with an aqueous core and a phospholipid bilayer, are one kind of nanoparticle. Modified liposomes with EAs or permeation enhancers make up the transferosomes. Therefore, these superior liposomes may distort themselves and enter skin pores that are 5–10 times smaller than their real width without noticeably inducing premature drug release. Therefore, these vesicles are a preferable option for delivering antifungal drugs over the epidermal barrier in order to improve therapeutic effectiveness.

4. Patents on Fungal Infection Treatment

Numerous patents that demonstrate developments in antifungal therapies have resulted from the creation of novel technologies and therapies for fungal infections. A thorough analysis of a few noteworthy patents that show different approaches to treating fungal infections may be found below.

Table 3: List of notable patents for fungal infection treatment:

Patent Name	Assignee	Grant Date	Description	Patent Number
Glyphosate-Based Antifungal Treatments	Monsanto Technology LLC	March 3, 2020	Although primarily focused on plant fungal pathogens, this patent offers insights into the broader application of glyphosate in fungal infection management.	US10575526B2
Antipathogenic Devices and Methods	Sintx Technologies, Inc.	June 25, 2024	This patent discloses compositions and methods involving silicon nitride coatings and slurries to inactivate pathogens, including fungi, bacteria, and viruses. The invention provides a multipurpose antipathogenic surface coating that can be applied to medical devices, potentially reducing hospital-acquired fungal infections.	US12017912B2
Method of Physical Antimicrobial Treatment	Nms Technologies Co., Ltd.	October 19, 2016	This patent describes the use of organosilicon bis-quaternary ammonium salts in antimicrobial films. These films, with a particle size of 1–1000 nm, exhibit antifungal activity, offering a novel approach to physical antimicrobial treatment in healthcare and industrial settings.	JP6010224B2

Antifungal Topical Composition	Blueberry Therapeutics Limited	March 2, 2022	This invention covers nanoparticle-based topical compositions for the treatment of fungal infections of the skin and nails. The patent emphasizes the use of polymeric nanoparticles to improve drug delivery and efficacy.	JP7028836B2
Antifungal Drugs and Their Use	Cidara Therapeutics Incorporated	March 28, 2018	This patent introduces new antifungal drugs and their applications. It focuses on chemical modifications of known compounds to improve their antifungal activity, stability, and target specificity.	JP6302108B2
Antifungal Drugs and Their Use	Middle Tennessee State University	March 29, 2022	Aurone compounds with antifungal and immunomodulatory properties. Aurone-based compounds are described in this patent as possessing antifungal and immunomodulatory properties. These compounds are suitable for treating fungal infections while also modulating the immune response.	US11286245B2
Niclosamide Formulations for Treating Disease	UNION Therapeutics A/S	May 10, 2022	Inhalable formulations for antifungal and antiviral uses. The patent includes inhalable formulations of niclosamide designed for antifungal and antiviral treatments. It proposes a novel delivery mechanism that enhances drug absorption and efficiency against fungal infections.	US11324708B1
Boron-Containing Small Molecules	Anacor Pharmaceuticals, Inc.	January 24, 2017	Improved topical antifungal solutions for nail infections. The invention focuses on boron-containing compounds as antifungal agents. These molecules are specifically designed to penetrate fungal cell walls and disrupt cellular function, making them effective for treating fungal nail infections.	US9549938B2
Treating Infection with Platelet-Targeting Nanoparticles	Regents of the University of California	January 18, 2022	Nanoparticle therapies target microbes, including fungi. This patent outlines the use of nanoparticles targeting platelets to prevent and treat infections caused by fungi and other microbes. The innovative approach ensures a localized and effective therapeutic response.	US11224577B2
Methods for Controlling Plant Pathogens	Monsanto Technology LLC	March 3, 2020	Glyphosate-based methods for fungal control in plants.	US10575526B2

Immunoglobulin for Fungal Infections	ADMA Biomanufacturing LLC	September 19, 2024	Human plasma-derived immunoglobulin compositions.	AU2021202598 B2

5. Transfersomes: **composition and structure**

The bilayer the structure of conventional liposomes can be altered to enhance their poor skin penetration (Romero & Morilla, 2013). Cevc and Blume were the first to modify liposomes by adding edge activators to the liposomal composition. The changed liposomes were referred to as "transfersomes," "elastic liposomes," or "deformable liposomes" (Cevc & Blume, 1992). Ultra-flexible vesicles with a bilayer structure are called transfersomes. By squeezing through the internal lipid of the stratum corneum, they can readily permeate the skin and get beyond the barrier function (El Zaafarany et al., 2010b). According to the osmotic gradient, Transfersomes migrate from the dry stratum corneum to a deeply hydrated layer after being applied to the skin. Their structure's surfactant aids in the lipid's solubilisation in the stratum corneum and enables the vesicles to penetrate deeply (Aljaeid & Hosny, 2016). Unlike conventional liposomes, transferosomes have a distinct structure with a hydrophilic outer layer and a hydrophobic inner layer that facilitates the drug's easier penetration of the barrier layers. They are made up of phospholipids and edge activators. Numerous non-intrusive formulations, such as gels, lotions, sprays, and patches, may be created using transferosomes. Additionally, transferosomes may be altered to enhance drug delivery; specifically, their size, charge, and composition can be changed to increase their stability and targeting capacity (Rakesh et al., 2021). Particle size can affect the stability, permeability, and interaction of transferosomes with target tissues or the epidermis. Vesicles with a diameter greater than 600 nm have generally been found to be incapable of penetrating the skin and releasing the medication they contain. As a result, particles smaller than 300 nm are believed to be suitable for topical medication administration (Fernández-García et al., 2020). Like liposomes, transferosomes are lipid-based vesicles that are more flexible and deformable. The following are the main elements of transferosomes:

• Phospholipids: Help encapsulate hydrophobic medications by forming the bilayer structure.

• Edge activators [EAs]: Surfactants that give the vesicles flexibility so they can pass through biological membranes, such as sodium cholate or Span 80 [30].

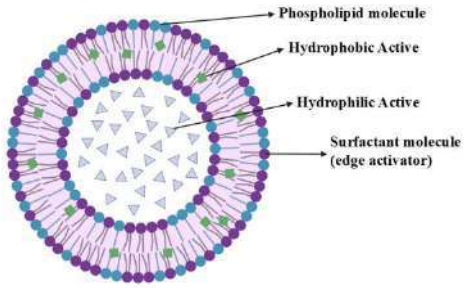

Figure 2: Structure of transferosomes

Sodium deoxycholate, sodium cholate, dipotassium glycyrrhizinate, Tween 80, Tween 60, Tween 20, Span 80, Span 65, and Span 60 are a few examples of edge activators that are utilised in

transfersomes (H. A. Benson, 2006). Because edge activators weaken their lipid bilayers, transfersomes exhibit increased deformability (H. Benson, 2009). Because transfersomes are more deformable and can readily pass through pores that are 5–10 times smaller than their diameter, they have a greater skin penetration rate than traditional liposomes (Hussain et al., 2017).

5. Mechanism of action of Transferosomes:

The term "transferosome," meaning "carrying body," is derived from the Latin word "transferred," meaning "to carry across," and the Greek word "soma," meaning "a body" (Opatha et al., 2020). One kind of transferosome that can be used as a transdermal drug delivery system is phospholipid vesicles. Transferosomes are synthetic vesicles that resemble cell vesicles in certain ways, which makes them suitable for controlled and potentially targeted drug delivery. Their construction allows them to act as both drug transporters and penetration enhancers, facilitating the passage of encapsulated drug molecules through the skin. Their main ingredients are water, phospholipid, and surfactant, which helps in better drug delivery (R. Gupta & Kumar, 2021). Because of its artificial membrane, which is softer, more flexible, and more configurable, transferosomes are said to be unique. gives the vesicle the ability to regulate and optimise itself. Furthermore, transferosomes may successfully overcome microporous barriers. Even if the pore size is less than the vesicle size, they can still get to the target location (Luiz et al., 2021) as seen in fig.3.

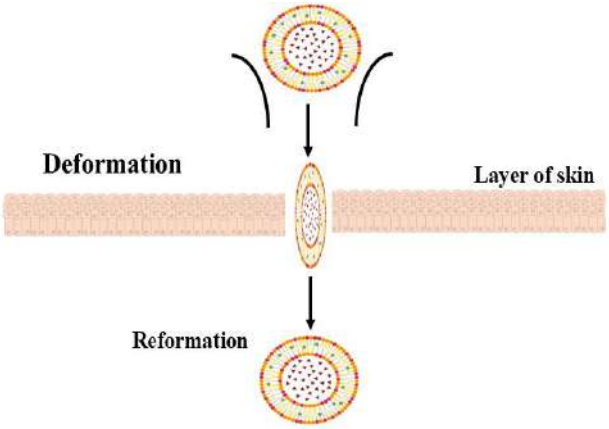

Figure 3: Mechanism of Action of Transferosomes.

Consequently, it can be said that the delivery of drugs via transferosomes is a safe and effective method. It is the ratio of certain surfactants to the overall amount of surfactants that controls the flexibility of the vesicle. Vesicular transferosomes are better for skin penetration than normal liposomes because they are more elastic. In order to overcome the barrier of skin penetration, these vesicles compress themselves along the intracellular sealing lipid of the stratum corneum (Bnyan et al., 2018; Reddy et al., 2015).

6. Antifungal Drugs Commonly Delivered via Transferosomes

Recent research has investigated the encapsulation of antifungal medications such as amphotericin B, fluconazole, and ketoconazole in transferosomes, which have shown enhanced permeability, stability, and therapeutic efficacy. In Sprague-Dawley rats, Pandit et al. examined the topical antifungal effectiveness of transfersomes loaded with miconazole nitrate. When compared to free drug solutions and standard liposomes, the developed modified liposomes demonstrated lower toxicity and higher in vivo antifungal activity (Pandit et al., 2014). An ideal FS-NTF formulation was created by Hala M. Alkhalidi utilising the Design Experiment paradigm. When

the nanotransfersome was implanted in a hydrogel matrix of hyaluronic acid, the drug released more quickly and the penetration parameters increased. This formulation is appropriate for local administration in the oral cavity and has demonstrated promising outcomes in both an in vivo ulcer index evaluation and an in vitro antifungal experiment. Its antifungal activity is increased by the combination of hyaluronic acid, sesame oil, and fluconazole. When incorporated in a cross-linked hyaluronic acid hydrogel and trapped in a nanotransfersome carrier, fluconazole can be administered for the treatment of oral candidiasis with efficacy (Alkhalidi et al., 2020).

Aggarwal and Goindi evaluated griseofulvin-loaded transfersomes in guinea pigs to eradicate dermatophytosis caused by Microsporum canis. When compared to traditional liposomes, the optimised transfersomal formulation demonstrated superior skin retention and penetration. After 10 days of treatment with griseofulvin-loaded transfersomes, histopathological investigation showed that all fungal spores had been eliminated from the skin of guinea pigs (Aggarwal & Goindi, 2012). Perez et al. recently created transfersomes loaded with amphotericin B (AmB), which were tested for human skin penetration and in vitro antifungal efficacy. They used Tween 80 as an edge activator and reported maximal deformability in transfersomes. Clinical isolates of Candida albicans showed a particularly high sensitivity to amphotericin B-loaded transfersomes in vitro when compared to mammalian cells. In comparison to a commercially available liposomal version of AmB (AmBisome), transfersomes demonstrated forty times greater accumulation in human skin (Perez et al., 2016).

7. Limitations and future prospects

Although transferosomes are thought to be a safer and more effective way to transport medications, this nano vesicular carrier system still has several drawbacks. These are chemically unstable because they are prone to oxidative deterioration, which may be considerably reduced by utilising purged gases, storing them at low temperatures, shielding them from light, and freeze-drying or spray-drying them after production (Grit & Crommelin, 1993; Iskandarsyah I et al., 2018). The purity of the natural phospholipids, which are crucial to the formulation, presents another drawback (van Hoogevest & Wendel, 2014). Furthermore, the expense of manufacture makes these compositions pricey. Notwithstanding these drawbacks, the increased effectiveness and tolerance brought about by the transferosomes' integration of antifungal medications has made room for more clinical research. Several studies show that the transferosomes have greater EE, lower particle size, and PDI. The phospholipid to EA ratio greatly influences the vesicle's deformability, which makes it simple to transport antifungal medication molecules into the skin's deeper layers without rupturing the biological membrane barrier. Furthermore, these vesicles can transport bigger molecules, protein peptides, and hydrophilic and hydrophobic molecules across the skin. Both topical and transdermal applications of these are undergoing testing. Since regular use of antifungal medicines might cause resistance, a reduced but still effective dosage can be administered locally to the location to reduce the likelihood of resistance developing later. A feasible platform for improving the transdermal delivery of antifungal medications is transferosomes. Compared to traditional administration systems, their special qualities have the potential to increase effectiveness, flux, sustained release, site specificity, and safety. To properly investigate the therapeutic potential of this technology, further research is necessary.

CONCLUSION

Mycoses, or fungal infections, are eukaryotic in nature, enabling them to infect eukaryotic hosts, causing superficial, subcutaneous, or systemic

infections. While typically cutaneous, these infections can become systemic in immunocompromised individuals, increasing morbidity and mortality. Antifungal agents are crucial for treatment; however, their widespread use has led to the emergence of drug resistance. Conventional antifungal formulations often exhibit poor oral bioavailability due to lipophilic properties and limited penetration of the stratum corneum, even when incorporated into nano-delivery systems such as liposomes, niosomes, and transferosomes. Transferosomes are ultra-deformable vesicular carriers, have demonstrated potential for enhanced transdermal drug delivery. Their deformability facilitates passage through biological membranes, enabling deeper penetration. The key features including small size, low polydispersity index (PDI), high encapsulation efficiency (EE), and sustained release profiles, make them promising candidates for antifungal drug delivery. Transferosome encapsulation enhances antifungal agent transdermal penetration, permeation, and bioavailability. It may also reduce drug toxicity and enhance safety profiles, making transferosomes a viable alternative to conventional methods for improved efficacy, flux, sustained release, site specificity, and safety. However, this review is beneficial for *in-vivo* paving new horizons towards developing advanced antifungal formulations.

LIST OF ABBREVIATIONS

EAs: Edge Activators
EE: Entrapment efficiency
PDI: Polydispersity index
AmB: amphotericin B
NPs: Nanoparticles
FIs: Fungal Infections

DECLARATIONS

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Authors contribution statement

Yashmi Jain: Writing – original draft, review & editing, Conceptualization. Dakshita Dutta: Writing – review & editing. Manish Yadav: review & editing, Supervision.

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