



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Review article

Present scenarios and future prospects of herbal nanomedicine for antifungal therapy



Rahul Yadav^a, Madhulika Pradhan^b, Krishna Yadav^{c,d}, Anand Mahalvar^a, Homesh Yadav^{a,*}

^a ISBM University, Nawapara, Gariyaband, Chhattisgarh, 493996, India

^b Rungta College of Pharmaceutical Education and Research, Kohka-Kurud Road, Bhlai, Chhattisgarh, 490024, India

^c University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, 492010, India

^d Raipur Institute of Pharmaceutical Education and Research, Sarona, Raipur, Chhattisgarh, 492010, India

ARTICLE INFO

Keywords:

Fungal infection
Antifungal compounds
Herbal extract
Essential oils
And nanocarriers

ABSTRACT

The current COVID-19 epidemic is a sobering reminder that human susceptibility to infectious diseases remains even in our modern civilization. After all, infectious diseases are still the major reason of death globally. Healthcare authorities have often underestimated and ignored the threat posed by “microbial dangers,” although they put millions of lives at risk every year. Overlooked developing diseases including fungal infections (FIs) contribute to roughly 1.7 million fatalities per year. As many as 150 million cases of severe and potentially life-threatening FIs are reported each year. In the last few years, the number of instances has steadily increased. Most of them are invasive fungal infections that require specialized treatment and hospital care. In recent years herbal antifungal compounds have been explored to acquire effective and safe therapy against fungal infections. However, potential therapeutic effects are hampered by the poor solubility, stability, and bioavailability of these important chemicals as well as the gastric degradation that occurs in the gastrointestinal tract. To get around this issue, researchers have turned to novel drug delivery systems such as nanoemulsions, ethosomes, metallic nanoparticles, liposomes, lipid nanoparticles, transferosomes, etc by improving their limits, nanocarriers can enhance the medicinal effects of herbal oils and extracts. The present review article focuses on the available antifungal agents and their characteristics, mechanism of antifungal drugs resistance, herbal oils and extract as antifungal agents, challenges in the delivery of herbal drugs, and application of nano-drug delivery systems for effective delivery of antifungal herbal compounds.

1. Introduction

The existing COVID-19 outbreak serves as a depressing reminder that infectious disease vulnerability exists even in modern civilization [1]. After all, infectious diseases remain the leading cause of death worldwide. Even though “microbial hazards” put millions of lives at risk every year, healthcare authorities have frequently underestimated and neglected the damage they pose [2]. FIs are one of the most commonly overlooked emerging diseases, accounting for nearly 1.7 million deaths each year. Every year, up to 150 million cases of severe and potentially fatal FIs are documented. The number of cases has progressively climbed during the last few years. The majority of them are invasive fungi that necessitate specific treatment and hospitalization [3,4]. FIs can range in severity from superficial (affecting only the skin) to systemic (affecting multiple organs).

The high mortality and morbidity rates associated with invasive fungal infections place a major strain on healthcare systems [5]. Rates of opportunistic infections in immunocompromised patients, such as AIDS, those whose immune systems have been suppressed to avoid organ rejection, and those undergoing immunosuppressive chemotherapy or immunosuppressive therapy for autoimmune conditions, are particularly concerning [6,7]. In terms of mechanism of action, there are four broad types of currently available drugs for treating invasive fungal infections: echinocandins, polyenes, azoles, allylamines, and allylamines [8,9]. Azoles prevent the fungal cell wall to form sterol (ergosterol) by obstructing the oxidative enzymes of the fungal cell membrane. This leads to incomplete synthesis and enhanced permeability of the fungal cell wall. While, echinocandins prevent the formation of key polysaccharides (1,3-β-glucan) of the fungal cell wall, and polyenes directly interact with the ergosterol and pass inside the fungal cell by

* Corresponding author.

E-mail address: homeshyadav@gmail.com (H. Yadav).

<https://doi.org/10.1016/j.jddst.2022.103430>

Received 27 February 2022; Received in revised form 8 May 2022; Accepted 10 May 2022

Available online 13 May 2022

1773-2247/© 2022 Published by Elsevier B.V.

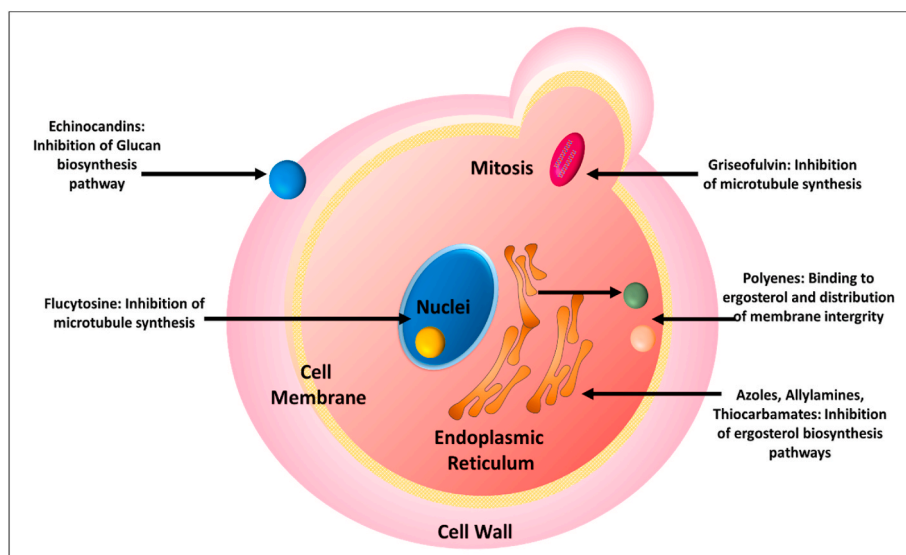


Fig. 1. Mechanism of action of various antifungal drugs.

creating pores, leading to leakage of cellular organelles from the cell causing cell death [10]. However, there are a variety of side effects associated with the use of topical antifungal medications for the treatment of fungal infections, such as burning and redness at the site of application [11]. In some cases, treatment may need to be continued due to the rapid drug release causing limited drug penetration. Likely, these drugs won't go to where they're supposed to, leaving the illness unattended. Additionally, antifungal resistance is again the cornerstone of new therapeutic methods for antifungal infections because it affects all of the currently available antifungal treatments [12].

Antifungal medicines derived from natural plant extracts and oils may be a viable solution to this problem. Antifungal properties of many plants, including *Vangueria infausta*, *Bucida buceras*, *Olinia ventosa*, *Breonadia salicina*, *Harpephyllum caffrum*, and *Xylothea kraussiana*, have been studied [13]. Cinnamon, peppermint, anise, citronella, pepper, clove, and camphor EOs, on the other hand, have been used in the creation of antimycotic medications because of their potent antifungal properties [14]. However, potential therapeutic effects are hampered by the poor solubility, stability, and bioavailability of these important chemicals as well as the gastric degradation that occurs in the gastrointestinal tract. To get over herbal extracts' drawbacks, new drug delivery systems have been developed as adaptable assemblies. Additionally, the resistance mechanisms could be avoided by encapsulating antimicrobial bioactive inside nanoparticles [15].

To get around this issue, researchers have turned to novel drug delivery systems such as nanoemulsions, ethosomes, metallic nanoparticles, liposomes, lipid nanoparticles, transfersomes, etc by improving their limits, nanocarriers can enhance the medicinal effects of herbal oils and extracts. The present review article focuses on the available antifungal agents and their characteristics, mechanism of antifungal drugs resistance, herbal oils and extract as antifungal agents, challenges in the delivery of herbal drugs, and application of nano-drug delivery systems for effective delivery of antifungal herbal compounds.

2. Available antifungals agents and their characteristics

Antifungal agents comprise azoles and polyenes, as well as benzylamines and methylamines. To treat fungal infections other than triconazole, ketoconazole, econazole, miconazole, and terbinafine, clotrimazole, and amorolfine are also commonly prescribed. Shampoo containing ketoconazole is used for fungal infections of the scalp. Depending on the kind of fungal infection, amphotericin, micafungin, itraconazole, flucytosine, anidulationfungin, voriconazole, caspofungin,

and injections are also available [16].

Both imidazoles and triazoles are antifungal azoles. Both function by blocking the enzyme lanosterol 14- α -demethylase, which stops the translation of lanosterol into ergosterol, causing the fungal cell wall to become porous. Both groups reveal their activity at distinct locations in the spectrum and have structural differences: imidazole is made up of two nitrogen atoms, whereas triazole has three [10]. Aspergillosis and mucormycosis are among the most prevalent fungal infections that can be treated with polyene antifungals such as nystatin and amphotericin B. Because ergosterol is the primary membrane sterol, polyene antifungals generate a polyene-ergosterol complex, which opens up pores and increases cell permeability. Despite this, amphotericin B has fungicidal efficacy against *Histoplasma capsulatum*, *Candida species*, *Blastomyces*, *Coccidioides immitis*, and *Cryptococcus neoformans*, however active therapy depends on criteria such as the medication dosage and pH. (6.0–7.5). It falls under the polyene class and is efficient against candida infections on the mucous membrane, but less effective against dermatophytes on the skin [8,17].

Dermatophytosis is treated with butenafine and allylamines, two forms of benzylamine medicines. Ergosterol production is disrupted by the inhibition of the production of the squalene epoxidase enzyme, which inhibits ergosterol production. Although allylamines are considered to be less effective antifungal drugs, they have a distinct benefit in the treatment of tinea pedis. As a second-line therapy option, oral antifungal medicines such as fluconazole, griseofulvin, and terbinafine are commonly utilized, with allitraconazole being found to be particularly beneficial [18,19].

Various antifungal drugs and their mode of action have been depicted in Fig. 1.

3. Mechanism of antifungal drugs resistance

Clinical and microbiologic resistance, or any combination of the two, are two ways to characterize antifungal resistance. Infectious organisms and pathogens are stated to be resistant to antimicrobial agents if their growth is hindered by concentrations higher than those seen in wild-type strains. When an antimicrobial agent is inhibiting the infecting organism at a concentration that is linked with a high risk of treatment failure, clinical resistance is said to exist [19,20]. Antibiotic resistance can be defined as the ability of an organism to evade typical concentrations of an antibiotic and/or to demonstrate a minimum inhibitory concentration (MIC) that falls within the range where particular mechanisms of resistance are likely and clinical benefit has not been reliably

demonstrated in treatment studies [21,22]. Fungi have adopted a variety of ways for drug resistance and the main mechanisms against azoles, echinocandins and polyenes have been discussed below in detail.

3.1. Mechanisms of resistance to azoles

Azoles interfere with the cellular synthesis of ergosterol, a key element of the fungal cell membrane. Azole drugs prevent lanosterol 14- α -sterol-demethylase and stop the translation of lanosterol into ergosterol. As a result, the level of ergosterol in the cell membrane drops, and ultimately cellular structure and function are altered, which inhibits fungal growth [22].

Candida species are resistant to azole antibiotics in a variety of ways. To begin with, the stimulation of efflux pumps within the fungal cell reduces drug concentration at the enzyme target, decreasing *Candida*'s susceptibility to azole antifungals or its ability to overcome its resistance to them [23]. Azole resistance in *Candida albicans* and *Candida dubliniensis* has been linked to increased expression of efflux pumps expressed by the MDR or CDR genes. Mutations in the ERG11 encoding gene are another characteristic pathway of resistance in *Candida* species, resulting in a changed target with reduced affinity for or incapability to bind azoles. *Candida* azole resistance could also be caused by an increase in the expression or upregulation of the changed target enzyme. In some cases, this might lead to azole medicines binding poorly to certain targets [24]. The establishment of bypass routes, which negate the membrane-disrupting effects of azole medications and are associated with decreased fungal growth, is the final possible mechanism of azole resistance in *Candida* species. In some resistant *Candida* strains, the ERG3 gene has been mutated, which may explain this [25].

3.2. Mechanisms of resistance to echinocandin

Echinocandins block the manufacture of 1,3-D-glucan, a critical component of the fungal cell wall, by interfering with the function of 1,3-D-glucan synthase. As a result, yeasts develop a faulty cell wall, which can lead to cell instability and lysis, while molds develop abnormal hyphal development. *Candida* resistance to echinocandins has been linked to mutations in a gene that encodes components of the 1,3-D-glucan synthase complex. Point mutations in the gene encoding the main and presumed catalytic component of 1,3-D-glucan synthase have been associated with lower susceptibility or resistance of *Candida* to echinocandins. *C. krusei*, *C. tropicalis*, *C. glabrata*, and *C. dubliniensis* have shown this resistance mechanism [22,26]. Echinocandin resistance in *C. glabrata* has been linked to FKS2 gene mutations. Glucophase synthase enzyme activity is altered by FKS mutation, which results in a higher 50% inhibitory concentration (IC50) [10,27].

3.3. Polyene resistance

Polyenes, which include amphotericin B and nystatin, are the earliest antifungal drugs. When polyene drugs interact with fungal-specific ergosterol in the plasma membrane of fungi, they produce concentration-dependent channels that kill cells and allow ions to escape, resulting in cell death. Cells in extramembranous aggregates may be killed through the extraction of ergosterol from the lipid bilayers by amphotericin B [22,28].

Resistance to Amphotericin B is frequently selected during therapy for species that are essentially less vulnerable. In most circumstances, Amphotericin B is fungicide. *Fusarium* spp, *Trichosporon* spp, *A. nidulans*, *Sporothrix schenckii*, *Scedosporium* spp, *A. terreus*, *A. calidoustus*, *A. flavus*, and *A. lentulus* are all amphotericin B-resistant species [29]. Resistance to polyenes is mediated by a decrease in cellular ergosterol concentration. Polyene resistance can be conferred by treatment with an azole antifungal that reduces cellular sterol concentrations [30,31].

4. Herbal oils and extract as antifungal agents

4.1. Herbal extracts

Plant extract is a general term used for a product of natural origin whose chemical constituents have not been expounded. A variety of extracts have exhibited explicit antifungal activity including *Curcuma zedoaria* [32], *Plectranthus barbatus*, *Hydrocotyle bonariensis*, *Lippia alba*, *Aristolochia cymbifera*, *Hydrocotyle bonariensis*, *Plectranthus amboinicus*, *Herreria salsaparilha* [33,34], *Mentha X piperita*, *Justicia pectoralis*, *Calamintha ascendens*, *Eleutherine bulbosa*, *Albizia inundata*, *Baccharis trimera*, *Plectranthus grandis*, *Cymbopogon citratus*, *Bauhinia forficata* [35, 36] and *Euphorbia hirta* L. [37].

The initial discovery of phytochemicals in *Carya illinoensis* leaves by Bottari et al. led to the development of plant extracts with antifungal properties against *Candida* species with MIC values ranging from 25 mg/mL to 6.25 mg/mL. Some of the efficacy against *Candida* strains was probably a result of the phenolic acids, flavonoid (rutin), and tannin compounds (catechin and epicatechin) [38]. *In vitro* biofilms developed by *Candida tropicalis* (fluconazole-resistant) significantly reduced when the berberine was isolated from natural herbs like *Coptis chinensis*, *Phellodendron amurense*, *Berberis aristata*, *Berberis vulgaris*, *Berberis aquifolium*, and *Tinospora cordifolia*'s roots, rhizomes and treated with the test fungal strain [39].

Some plants in the Lamiaceae family were studied by Waller and his colleagues for their antifungal properties. Antifungal activity was found in the extracts and EOs of 55 botanical species belonging to 27 genera. Plants belonging to the Lamiaceae family were found to be *in vitro* susceptible to pathogenic fungus of *Candida* spp, *Aspergillus* spp., *Malassezia* and *Cryptococcus* spp., *Sporothrix* spp, *Epidermophyton* spp., *Microsporium* spp, *Trichophyton* spp [40]. Recently, Barros and their group reported that ethanolic extracts of stems, leaves, and rhizomes of *Chamaecostus cuspidatus* against *Candida* and *Trichophyton* species and reported good antifungal activity [41]. In another study, Terças found antifungal effects in the leaf extract of *Terminalia catappa* when tested against *Candida* spp [42].

In vitro studies by Akroum et al. indicated that *Vicia faba acetylic* extract had antifungal activity against *C. albicans* (MIC 0.010 mg/mL). Moreover, the extract (20 g/mL) reduced mortality in mice with candidiasis after administration [43]. Todorovic et al. examined polyphenols of powders of *Theobroma cacao* against *C. albicans*. They reported good antifungal activity by the extract with a MIC of 5.0 mg/mL [44]. Numerous more plants, in addition to those listed above, are being studied for antifungal properties. Even though screening plant extracts can speed up the discovery process, research has focused on the identification of chemical components. Crude extract research may be the first stage in discovering a new promising drug, which is followed by an identification of the chemical components responsible for the antifungal action.

4.2. Essential oils (EOs)

Essential oils (EOs) are combinations of volatile components that can be found in various plant sections (flowers, bark, leaves, fruits, and rhizomes). Steam distillation is the most common method for extracting these oils. Mono- and sesquiterpenes and phenylpropanoids are the main components of EOs, which are responsible for the plant's olfactory qualities, as well as its ability to fight off microbes [45]. EOs cause yeast cell wall damage by creating a potential gradient across the cell wall and disrupting ATP synthesis [46]. The ability of EOs to infiltrate and tear fungal cell walls and protoplasm membranes facilitates the disintegration of mitochondrial membranes. In the electron transport chain, a modification in the flow of electrons can lead to this. Cells infected with fungi may have their lipids, proteins, and supermolecules damaged as a result of this. The microbe and fungal cell walls as well as the living material membrane are destroyed by the oil elements, resulting in an

Table 1
List of herbs and their antifungal potential against various fungi.

S-N.	Name of the plant	Family	Parts used	Chemical compound	Microorganism tested	References
	<i>Eugenia uniflora</i>	Myrtaceae	Leaves	Sesquiterpenes, Monoterpene, hydrocarbons	<i>C. albicans</i> , <i>C. dubliniensis</i> , <i>C. glabrata</i> , <i>C. krusei</i>	[54]
	<i>Psidium guajava</i>	Myrtaceae	Leaves	beta-caryophyllene and caryophyllene oxide	<i>Fusarium moniliforme</i> , <i>Rhizoctonia solani</i> and <i>Helminthosporium oryzae</i>	[55]
	<i>Curcuma longa</i>	Zingiberaceae	Rhizome	Turmeric oil	<i>Cladosporium cladosporioides</i> , <i>F. graminearum</i> , <i>Alternaria</i> <i>alternate</i> , <i>F. tricinctum</i> , <i>F. chlamydosporum</i> , <i>Botrytis cinerea</i> , <i>Sclerotinia sclerotiorum</i> , <i>F. culmorum</i> , <i>Rhizopus oryzae</i> ,	[56]
	<i>Cassia occidentalis</i>	Fabaceae	seed	<i>Hydroxy anthraquinone</i>	<i>M. gypseum</i> , <i>Trichophyton mentagrophytes</i> <i>Microsporium nanum</i> , and <i>T. terrestre</i> .	[57]
	<i>Asparagus racemosus</i>	Asparagaceae	leaves	<i>Saponin</i>	<i>M. gypseum</i> , <i>M. nanum</i> , <i>T. mentagrophytes</i> and <i>T. terrestre</i> .	[57]
	<i>Schinus terebinthifolius</i>	Anacardiaceae	Stem bark	Extract	<i>C. glabrata</i> , <i>C. albicans</i> , <i>C. krusei</i> ; and <i>C. tropicalis</i>	[58]
	<i>Persea americana</i>	Lauraceae	Leaves	Chromene	<i>Candida</i> spp, <i>Cryptococcus neoformans</i> and <i>Malassezia</i> <i>pachydermatis</i>	[59]
	<i>Parapiptadenia rigida</i>	Fabaceae	Stem bark	Pyrrolidine amide	<i>C. albicans</i>	
	<i>Ajania fruticulosa</i>	Asteraceae	Leaves	camphene, 1,8-cineole, α - and β -thujone	<i>A. carbonarius</i> and <i>Aspergillus niger</i>	[60]
	<i>Mimosa tenuiflora</i>	Mimosaceae	wood	Sesquiterpene lactone	<i>C. albicans</i> and <i>Cryptococcus neoformans</i>	[61]
	<i>P. regnellii</i>	Piperaceae	Leaves	Extract	<i>Trichophyton mentagrophyte</i>	
	<i>Tithonia diversifolia</i>	Asteraceae	Whole plant	saponins, Polyphenols	<i>Chlorella fusca</i> and <i>M. violaceum</i> ,	[62]
	<i>Vernonanthura</i>	Asteraceae	Root	Extracts	<i>T. mentagrophytes</i>	[63]
	<i>Zingiber officinale</i>	Zingiberaceae	Rhizomes	Steroidal saponin	<i>F. verticillioides</i>	[64]
	<i>Datura metel</i>	Solanaceae	Whole plant	Diterpenoid, Alkaloids	<i>M. canis</i> , <i>T. longifusus</i> , <i>C. albicans</i> , <i>A. flavus</i> , and <i>F. solani</i> ,	[65]
	<i>Cassia tora</i>	Leguminosae	Seeds	Anthraquinone	<i>B. cinerea</i> , <i>Phytophthora infestans</i> ,	[66]
	<i>Rubia tinctorum</i>	Rubiaceae	Root	Triterpene	<i>P. Alternaria</i> , <i>A. niger</i> , <i>Mucor mucedo</i>	[67]
	<i>Chamaecyparis pisifera</i>	Cupressaceae	Leaves and Twigs	Isoflavone	<i>P. oryzae</i>	[68]
	<i>Prunus yedoensis</i>	Rosaceae	Leaves	Diterpenes	<i>C. herbarum</i>	[69]
	<i>Calea uniflora</i>	Asteraceae	Underground parts	senecioid	<i>Candida</i> spp.	[70]
	<i>Clinacanthus nutans</i>	Acanthaceae	Ariel parts	<i>Megastigmanes</i> 1, 2, 7, and 8	<i>Candida albicans</i>	[71]
	<i>Phytolacca tetramera</i>	Phytolaccaceae	Berry, leaf and root extracts	<i>Phytolaccagenin</i> and <i>phytolaccoside B</i>	<i>Candida albicans</i> and <i>Candida glabrata</i>	[72]
	<i>Thevetia peruviana</i>	Apocynaceae	Leaf extract	Alkaloids, steroids, volatile oils, flavonoids, and tannins	<i>Alternaria solani</i>	[73]
	<i>Vitis vinifera</i>	Vitaceae	Berry Skins, Seeds, Leaves, and Stems extract	Phenols and Polyphenols	<i>Candida albicans</i> , <i>Candida glabrata</i> , <i>Candida tropicalis</i> , <i>Candida parapsilosis</i> and <i>Candida dubliniensis</i>	[74]
	<i>Scutellaria baicalensis</i>	Lamiaceae	Root extract	<i>Baicalein</i>	<i>Trichophyton rubrum</i> , <i>Trichophyton mentagrophytes</i> , <i>Aspergillus</i> <i>fumigatus</i> , and <i>Candida albicans</i>	[75]
	<i>Primula macrocalyx Bunge</i>	Primulaceae			<i>Candidaalbicans</i> , <i>Aspergillus niger</i> , <i>Saccharomyces kudriavzevii</i> , <i>Penicillium chrysogenum</i> , <i>Candida parapsilosis</i> , <i>Candida rugosa</i> , <i>Candida tropicalis</i> and <i>Rhizopus stolonifer</i>	[76]

overly run protoplasm and its actions [47]. The EOs have been employed for a wide variety of plant pathogens. The EOs extracted from several plants such as *Allium cepa*, *Eugenia caryophyllata*, *Curcuma longa*, *Ocimum basilicum*, *Moringa olifera*, *Cymbopogon*, *Thymus vulgaris* and *Salvia rosmarinus* have shown significant antifungal activity against a large variety of fungi [48].

Some EOs, such as yarrow oil, pepper oil, cinnamon oil, and carrot oil, are more potent against fungi than bacteria. *C. suvabenium* essential oil was reported effective against *Trichophyton mentagrophytes*, *Microsporium canis*, and *T. rubrum*, along with *C. albicans* and *C. glabrata* with a MIC of 0.47–2.52 g/ml [49]. *E. citriodora* EOs from Algerian *E. citriodora* leaves was shown to have a stronger antifungal potential against the investigated microorganisms, with MFC ranging from (0.6–5L/mL and 1.25–5L/mL) respectively [50]. Antifungal properties of *Rosmarinus officinalis* EOs (REO) against *A. flavus* have recently been studied by da Silva and his team. MIC and MFC were both reported to be 500 g/mL. At a dosage of 250 g/mL, REO also repressed the growth of *A. flavus* [51].

Maccioni and the group explored the antifungal activity of essential oil from *Teucrium capitatum* L. and reported that the sample significantly inhibited *C. albicans* [52]. Ghasemi and colleagues tested the antifungal potential of Artemisia Siebert's EOs composition against *Botrytis cinerea*. When tested at concentrations of 1000 and 1500 ll-1, they found

that A. Siebert's essential oil considerably slowed the test microorganism's mycelial development. They concluded that the tested essential oil has good antifungal properties [53]. Apart from the above discussed antifungal herbal extracts and EOs other antifungal herbal constituents showing effectiveness against various fungi have been elaborated in Table 1.

5. Challenges in the delivery of herbal drugs

Because of their delicate structure, most herbal extracts are vulnerable to exposure to moisture, light, air, heat, metal ions, and pH variations. Therefore, they are unable to continue their operations for the duration of their designated shelf life. Because of their sensitivity to light, heat, and oxygen bioactive quickly oxidized and damaged, and hence lose their active properties. The main drawbacks of herbal extracts are related to their ability to penetrate and reach their target cells and organs in the active form [77–80]. To use herbal extracts in a drug delivery system, their low permeability and low solubility must be taken into consideration. Permeability and solubility issues of herbal extracts have been the subject of numerous investigations [80,81]. Many herbal bioactives such as resveratrol, curcumin, naringenin, etc have limited solubility in water and lipophilic solutions, meaning that it has low

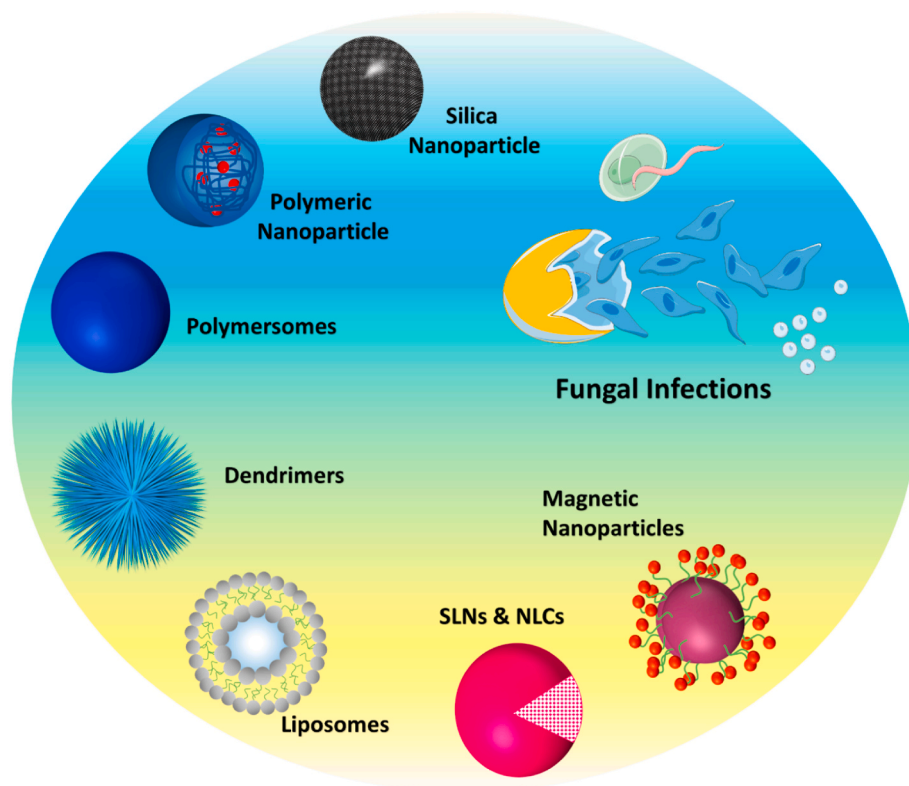


Fig. 2. Nanocarriers employed for the delivery of herbal bioactive and essential oils.

bioavailability and cannot reach the organ or cell it is intended to benefit. As a solution, new drug delivery carriers have been created to address these issues and constraints, as well as to increase bioavailability and therapeutic efficacy [82].

6. Herbal NDDS against fungal infection

To solve the shortcomings of conventional drug delivery methods, NDDS employs a revolutionary approach to drug delivery. Many unique herbal formulations have been described using proactive and plant choices, including nanocapsules, liposomal delivery systems, microsphere-based delivery systems, and ethosome-based delivery systems. The major advantages of the novel formulation over conventional formulations, include enhanced solubility, enhanced bioavailability, protection from toxicity, improved cellular distribution, constant delivery, shielding from physical and chemical breakdown, enhanced pharmacological activity, and improved stability [83]. Incorporating natural medicines into modern dose forms allows them to be administered more appropriately and effectively. Novel herbal medicine delivery systems employing liposomes, SLNs, polymeric nanoparticles, NLCs, metallic nanoparticles, etc can be developed to achieve this specifically for the treatment of fungal infections (Fig. 2) [84]. Various novel drug delivery systems used for encapsulating herbal extracts and EOs for antifungal treatment have been elaborated below.

6.1. Liposomes

For the preservation of natural antimicrobials, liposomes are among the most widely investigated lipid-based nanostructures. Liposomes are self-assembled closed vesicular structures constituted from one or more lipid bilayers that distinguish them from the adjacent aqueous milieu [85–87]. Liposomes have an amphiphilic character, and as a result, these structures can be utilized to encapsulate chemicals of different polarities [88,89].

In this context, Dave and the team formulated liposomal gel enriched with neem extract and ketoconazole for the effectual treatment of seborrheic dermatitis. They developed liposomes by thin-film hydration method $88.9 \pm 0.7\%$ drug entrapment with 141.6 nm particle size of optimized liposomes. The anti-fungal activity of liposomal formulation exhibited good antifungal activity against *A. niger* and *C. tropicalis* with an inhibition zone of 8.9 and 10.2 mm, respectively. Overall, they concluded that the developed novel gel could have great antifungal potential and synergistic effect on seborrheic dermatitis [90]. Mittal and group developed PEGylated Curcumin nanoliposomes and reported a 1000-fold enhancement in curcumin hydrophilicity and a tenfold increase in drug stability. Overall findings confirmed enhanced bioactivity of nano curcumin than plain curcumin suggesting curcumin nanoliposomes to be an effective modality to treat fungal and other infectious diseases [91].

6.2. Solid lipid nanoparticles (SLNs)

SLNs are nanoparticle constituted from one or more solid lipids. Their diameter ranges from 50 to 1000 nm, they don't require organic solvents for synthesis, they are inexpensive, and they can be easily scaled up. They are fascinating lipid-based carriers for several reasons [92]. Because of this, SLNs were created to circumvent the drawbacks of previous lipid-based nanocarriers. Substitution of liquid oil was done with solid oil, which had an ordered crystal structure and so allowed the bioactive components to be contained inside the matrix of lipids, thereby making the emulsion more stable [93,94]. In this regard, Lima and the group developed phytol-loaded solid lipid nanoparticles (SLN) and assessed the antifungal efficacy of the formulation against different strains of *Candida* species. Phytol's MIC against 15 *Candida* species strains was significantly improved by the encapsulating phytol inside SLN. Finally, they suggested, that the developed SLN could be an efficient cargo for phytol transport in anticandidal therapy [95].

6.3. Nanostructured lipid carriers (NLCs)

NLCs are the carriers made from a mixture of solid lipids and liquid lipids, which boost loading capacity and limit bioactive ingredient ejection [96–98]. Lipids distributed in water provide the basis of these nanostructures, which have a solid to liquid lipid ratio of 70:30. Liquid lipids in NLCs, as opposed to SLNs, prevent the particle from merging with the solid matrix, allowing bioactive substances to be encapsulated and better solubilized. NLCs, on the other hand, is created from a mixture of lipid molecules that are spatially distinct, resulting in a matrix that is more prone to encapsulating bio compounds than SLNs [99–101]. In recent research, Baldim et al., encapsulated *Lippia sidoides* essential oil (LSEO) in NLCs and examined its antifungal activity against *C. auris*. Both the LSEO-loaded NLC and plain LSEO showed strong activity against the yeast and did not exhibit any toxicity in the in vivo model [102].

6.4. Ethosomes

It's a non-intrusive vesicular carrier made up of the following components: ethanol; phospholipids; and water. Because of the high quantity of ethanol contained in the carrier, the skin's lipid bilayer is easily disrupted by a soft, flexible carrier. Ethosomes, on the other hand, has been widely used in topical medication delivery for antifungal agents [103]. Shetty et al., developed clove oil-enriched ethosomal gel and assessed its effectiveness for the treatment of cutaneous candidiasis. Compared to pure clove oil, the ethosomal gel has acceptable antifungal efficacy against the pathogen *C. albicans*. Based on the results, the new formulation for clove oil administration could be a promising one for treating cutaneous candidiasis [104].

6.5. Nanoemulsions

Several active substances may be made more bioavailable through the use of a colloidal dispersion called a nanoemulsion. Nanoemulsions have excellent stability, rapid digestion, protection from degradation, controlled release, and a high ability to enhance the bioavailability of drugs. Because nanoemulsions are highly flexible, they can be used to transport a variety of different drug moieties. To create nanoemulsions with various physicochemical and biological features, lipids and oils such as triglycerides and EOs can be used to construct the oily phase. It is also possible to alter the aqueous portion by introducing various water-soluble components [105]. Das et al., developed chamomile EO (CPE) enriched pickering nanoemulsion and examined the antifungal potential of the antifungal nanoemulsion against the *Candida* species. CPE showed significantly higher antifungal activities and overall findings suggested that the applicability of CPE nanoemulsion as a potential delivery system to fight against fungal infections [106].

In research, Mahajan et al., obtained essential oil obtained from fresh leaves of *Ocimum gratissimum* and developed essential oil-based nanoformulations to explore its antifungal potential against *P. digitatum*. Stable *O. gratissimum*. With an average droplet diameter of 259.4 nm and sonication period of 10 min, essential oil-enriched nanoemulsions with a 1:1 (v/v) ratio of essential oil and surfactant were produced. *P. digitatum* spore germination and hyphal extension were suppressed by *O. gratissimum* essential oil nanoemulsions more effectively than by pure oil, according to the results [107].

6.6. Transfersomes

There has been a significant advance in the development of vesicular drug delivery systems using deformable liposomes (Transfersomes), which are lipid bilayer-enclosed, water-repellent nanoparticles with an edge activator. Recently, Kammoun and their group developed an in-situ gel loaded with voriconazole–clove oil nano-transfersomes (VRC–CO–NT) and evaluated its antifungal activity against *A. flavus*.

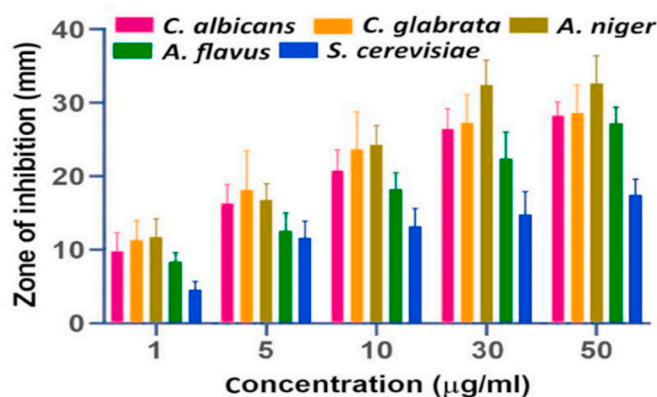


Fig. 3. Antifungal activity of ZnO NPs of five different fungal species. The results are presented as mean \pm standard deviation of zone of inhibition on agar plates (Adopted from Ref. [114]).

After 12 h, 82.5% of VRC was out from the optimized in situ gel, which resulted in a 5.4-fold improvement in drug penetration. An in-situ gel with VRC–CO–Transfersome loaded in it is a fundamental innovation in vesicular drug delivery devices that have one inner aqueous compartment enclosed by an edge activator lipid bilayer [108].

6.7. Metallic nanoparticles

When it comes to biological applications, metallic nanocarriers have been widely tested. Because of their small size, high surface area, ability to be surface modified, and high responsiveness towards living cells, they have achieved an extraordinary position in the field of diagnosis and drug delivery. When it comes to antifungal drug delivery, silver nanoparticles (AgNPs) are a common choice [109,110].

Mohammadi et al., investigated the potential of green synthesized silver AgNPs against *Candida albicans*. They adsorbed the plant extract on the surface of the pre-prepared AgNPs. To treat superficial fungal infections, the created AgNPs showed greater suppression of the test pathogen than fluconazole (FLZ), showing that the developed formulation is a suitable alternative to FLZ [111]. Nguyen and group developed AgNPs of leaf extracts of *Pouzolzia zeylanica*, *Scoparia dulcis* and *Phyllanthus urinaria*, namely *P. zey.*AgNPs, *S. dul.*AgNPs and *P. uri.*AgNPs, demonstrated antifungal capacity. *P. zey.*AgNPs, *S. dul.*AgNPs and *P. uri.*AgNPs, exhibited a good efficacy against *A. niger*, *Fusarium oxysporum*, and *A. flavus*, demonstrating their potential as antifungals [112].

Paul and their group developed, CUR–AgNPs to examine antifungal activity against fluconazole-resistant *Candida* spp. Isolated from HIV patients. Compared to silver nitrate and free CUR, CUR–AgNPs had a stronger antifungal activity against *C. glabrata*; *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. kefyr*; and *C. krusei* [113]. In another research, Karkhane and team developed Zinc oxide nanoparticles (ZnO–NPs) using aqueous extract of *Sargassum vulgare* (SVE) as a reducing and capping agent. The particle size of ZnO NPs ranged from 50 to 150 nm (diameter) with spherical configuration. The ZnO–NPs demonstrated wide-spectrum antifungal action against *Aspergillus*, *Candida* and *saccharomyces cerevisiae* (Fig. 3). However, the antifungal activity against *S. cerevisiae* was found to be moderate. The results of the well-diffusion assay established highest efficacy of developed formulation on *Candida* and *Aspergillus* species [114].

6.8. Polymeric nanoparticle

A polymeric nanoparticle is one in which the medicine has been dissolved, trapped, or somehow attached to the nanoparticle matrix. Nanocapsules (matrix-like structure) and nanospheres (core-shell

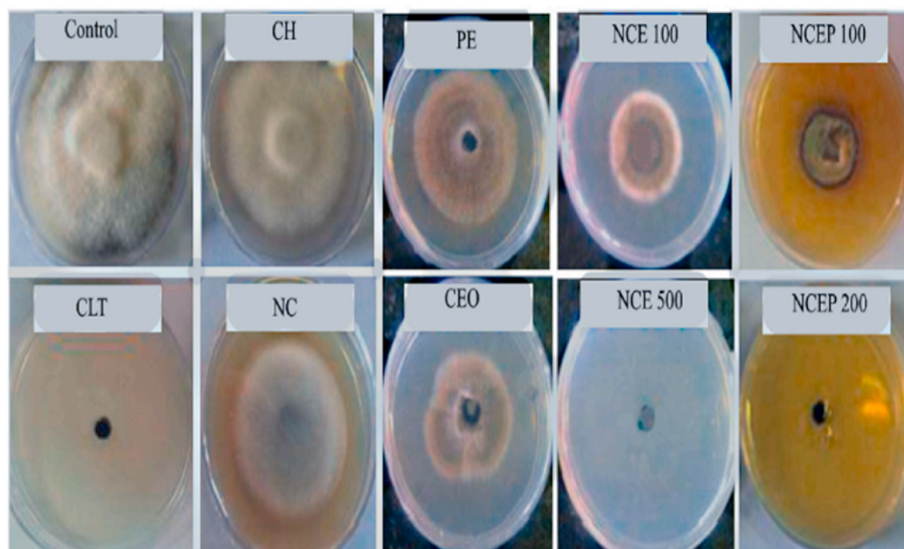


Fig. 4. Antifungal activity (against *A. Alternaria*) of control group, chitosan solution (CH), Chitosan nanoparticles, Peganum extract (PE), CEO loaded nanoparticles (NCE), PE-CEO loaded nanoparticles (NCEP), Carum essential oil (CEO), Chlorothalonil (CLT), Negative Control (Adopted from Reference [116]).

Table 2
Novel drug delivery carriers employed to encapsulate herbal antifungal extracts and essential oils.

SN	Nanocarrier	Herbal Constituent/Extract	Test Organism	Comment	References
	Liposomes	Garlic extract	<i>P. expansum</i> , <i>P. herquei</i> , <i>F. graminearum</i> , <i>A. niger</i> , and <i>A. flavus</i>	Enhanced antifungal potential of extract loaded liposome than free extract	[119]
	Liposomes	α -Bisabolol in combination with Fluconazole	<i>Candida albicans</i> , <i>Candida krusei</i> , <i>Candida tropicalis</i>	Liposomal bisabolol potentiated the antifungal effect of fluconazole against the test organism	[120]
	Liposomes	Essential Oil of Eucalyptus camaldulensis Leaf	<i>M. canis</i> , <i>M. gypseum</i> , <i>Trichophyton rubrum</i> and <i>T. verrucosum</i> ,	Enhanced antifungal potential of oil loaded liposome than free oil.	[121]
	Nanoliposomes	Artemisia annua L. essential oil (AEO)	<i>C. parapsilosis</i> , <i>C. krusei</i> , <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. albicans</i> , and <i>C. dubliniensis</i>	Minimum fungicidal concentration (MFC) of pure AEO was significantly higher than AEO-loaded nanoliposomes.	[122]
	SLNs	<i>Z. multiflora</i> essential oil-loaded solid lipid nanoparticles (ZE-SLNs)	<i>A. niger</i> , <i>A. ochraceus</i> , <i>A. flavus</i> , <i>Alternaria solani</i> , <i>Rhizopus stolonifera</i> and <i>Rhizoctonia solani</i> .	ZE-SLNs exhibited higher antifungal efficacy than ZEO.	[123]
	SLNs	Copaiba oil and allantoin	<i>Candida krusei</i> and <i>Candida parapsilosis</i> , <i>Trichophyton rubrum</i> and <i>Microsporium canis</i>	Improved antifungal activity of copaiba oil due to nanoencapsulation.	[124]
	NLCs	Palmarosa essential oil (PEO)	<i>Aspergillus nomius</i> .	100% of inhibition of fungal growth was reported.	[125]
	NLCs	Cinnamon Essential Oil	<i>Penicillium Citrinum</i> and <i>Penicillium Expansum</i>	Significant reduction in antifungal activity	[126]
	AgNPs	Fruit extract of Prunus cerasifera	<i>X. citri</i> , <i>P. syringae</i> , <i>A. niger</i> , <i>A. flavus</i> , <i>A. fumigatus</i> , <i>A. terreus</i> , <i>P. chrysogenum</i> , <i>F. solani</i> and <i>L. theobromae</i> .	Broad spectrum inhibition by test formulation in comparison to standard antimicrobial drugs against organism	[127]
	AgNPs	Rhizophora mucronate leaves extract	<i>C. albicans</i> , <i>A. fumigatus</i> , <i>A. flavus</i> and <i>Cryptococcus neoformans</i>	Enhanced antifungal activity of fluconazole in presence of extract loaded AgNPs	[128]
	AgNPs	Lawsonia Inermis extract	<i>Candida albicans</i> , <i>Microsporium canis</i> , <i>Propionibacterium acne</i> and <i>Trichophyton mentagrophytes</i>	Phenolic compounds showed strong fungicidal activity.	[129]
	AgNPs	Tropaeolum majus.	<i>Penicillium notatum</i>	Good antifungal activity against <i>Penicillium notatum</i> with MIC value 31.2 μ g/ml.	[130]
	AgNPs Copper nanoparticles (CuNPs) and Iron nanoparticles (FeNPs)	Green and black tea leaves extract	<i>Aspergillus flavus</i> and <i>A. parasiticus</i>	Green tea or black tea leaves extracts enriched Ag-NPs showed excellent antifungal property than FeNPs and CuNPs.	[131]
	Polymeric nanoparticle	Curcumin	<i>S. cerevisiae</i> , <i>A. niger</i> , and <i>Penicillium notatum</i>	Broad-spectrum antifungal activity was reported	[132]
	Lipid nanoparticle	Lippia sidoides essential oil	<i>C. albicans</i>	Enhanced antifungal activity was reported	[102]

morphology) can be formed depending on the organic phase's composition and manufacturing procedure [115]. Increasing the safety profile of these nanoparticles is their ability to transport proteins, DNA, and medications such as antifungals to cells and particular target organs in the body. Antifungal herbal ingredients have also been successfully delivered using PNPs.

In this context, Izadi and group developed *Carum copticum* essential oil (CEO) and *Peganum harmala* extract (PE) loaded chitosan nanoparticles to improve antifungal activity against *A. alternata*. The developed nanoparticles were spherical in shape having a mean size of 100 nm. CEO-PE enriched nanoparticles presented inhibitory at a concentration of 200 ppm, while plain essential oils and extracts exhibited

inhibitory concentrations at 500 and 750 ppm, respectively. *In-vivo* tests demonstrated that free chitosan solution, CEO-PE, CEO, PE, also exhibited good antifungal but significantly higher activity was reported for CEO-PE enriched nanoformulation (see Fig. 4). These results showed that CEO-PE loaded chitosan nanoparticles may successfully suppress pathogenic fungus in both *in vivo* and *in vitro* circumstances [116].

Using an olive leaf extract-loaded chitosan nanoparticle, Muzzalupo and coworkers recently tested the antifungal effect of the nanoparticles against the fungus *Fusarium proliferatum (in vitro)* (AACC0215). The larger concentration of extract-loaded nanoparticles tested against the target species proved to be highly effective, according to their findings. They found that both germination and growth were inhibited by 87.96 and 58.13%, respectively, according to their findings. The final thoughts were that these discoveries would allow for a reduction in the dosage of fungicides that might otherwise be detrimental to humans [117]. AgNPs were synthesized by Suwan and colleagues using an aqueous extract of *Psidium guajava* (PE). Poloxamer 407 polymeric micelles were used to further cover the AgNPs. They found that AgNPs-loaded polymeric micelles had great stability and good inhibitory efficacy against *C. albicans* [118].

Apart from the above-discussed nanocarriers, other nanocarriers used for the delivery of antifungal herbal constituents have been presented in Table 2.

7. Conclusions and future perspectives

Multidrug-resistant fungal strains are spreading, which necessitates the development of novel natural antifungal classes as well as a new and effective drug delivery technology. Due to the existence of active phytoconstituents, recent research on medicinal plants has revealed their significant pharmacological relevance. Due to high death rates associated with invasive mycoses and the need to create better fungicidal medications and thus reduce treatment lengths and costs, novel drug delivery vehicles encapsulating plant-based antifungals are being designed and developed.

As encapsulation technology and materials science have advanced, antifungal chemicals can be transported and released in a range of lipid, polymer, and metal nano-drug delivery systems. Natural antifungal chemicals can be effectively transported in these nanostructures because they can be manufactured to have different compositions, surface characteristics, and membrane fluidity. Nanostructures can contain hydrophobic, hydrophilic, and amphiphilic chemicals, making them excellent carriers for antifungal extracts and essential oils. Different researchers have been able to successfully encapsulate various antimicrobial peptides, enzymes, EOs, and antimicrobial phytoconstituents within lipid nanostructures. Different polysaccharides and proteins from biopolymers can also be incorporated into nanocarrier formulations, as well as metals such as silver and gold, resulting in increased stability and release properties and compatibility with various delivery systems. The development of nanocarriers that can be used in conjunction with traditional methods and/or that encourage prompted antifungal release is also useful to encourage microbial protection in healthcare and other sectors, even though herbal extracts and oils have been extensively studied using nanoencapsulation.

Funding

None.

Declaration of competing interest

None.

References

- [1] M. Pradhan, K. Shah, A. Alexander, Ajazuddin, S. Minz, M.R. Singh, D. Singh, K. Yadav, N.S. Chauhan, COVID-19: clinical presentation and detection methods, *J. Immunoassay Immunochem.* 43 (2022), 1951291, <https://doi.org/10.1080/15321819.2021.1951291>.
- [2] K. Kainz, M.A. Bauer, F. Madeo, D. Carmona-Gutierrez, Fungal infections in humans: the silent crisis, *Microb. Cell (Graz, Austria)* 7 (2020) 143–145, <https://doi.org/10.15698/mic2020.06.718>.
- [3] M. von Lilienfeld-Toal, J. Wagener, H. Einsele, O.A. Cornely, O. Kurzai, Invasive fungal infection, *Dtsch. Arztebl. Int.* 116 (2019) 271–278, <https://doi.org/10.3238/arztebl.2019.0271>.
- [4] F. Bongomin, S. Gago, R.O. Oladele, D.W. Denning, Global and multi-national prevalence of fungal diseases-estimate precision, *J. Fungi (Basel, Switzerland)* 3 (2017) 57, <https://doi.org/10.3390/jof3040057>.
- [5] F. Lantermier, S. Cypowyj, C. Picard, J. Bustamante, O. Lortholary, J.-L. Casanova, A. Puel, Primary immunodeficiencies underlying fungal infections, *Curr. Opin. Pediatr.* 25 (2013) 736–747, <https://doi.org/10.1097/MOP.000000000000031>.
- [6] D.A. Enoch, H. Yang, S.H. Aliyu, C. Micallef, The changing epidemiology of invasive fungal infections, *Methods Mol. Biol.* 1508 (2017) 17–65, https://doi.org/10.1007/978-1-4939-6515-1_2.
- [7] K. Yadav, M. Pradhan, D. Singh, M.R. Singh, Macrophage-associated disorders: pathophysiology, treatment challenges, and possible solutions, in: *Macrophage Target. Deliv. Syst.*, Springer, 2022.
- [8] S. Hasim, J.J. Coleman, Targeting the fungal cell wall: current therapies and implications for development of alternative antifungal agents, *Future Med. Chem.* 11 (2019) 869–883, <https://doi.org/10.4155/fmc-2018-0465>.
- [9] R.K. Aneshwari, K. Yadav, R.A. Banjara, A. Kumar, A. Kujur, V. Jain, Standardization and comparative evaluation of phytochemical content and antioxidant activity of *Alocasia indica* and *Tephrosia purpurea*, *Int. J. Health Sci.* (2022) 2241–2251, <https://doi.org/10.53730/ijhs.v6n2.5485>.
- [10] T.K. Mazu, B.A. Bricker, H. Flores-Rozas, S.Y. Ablordepey, The mechanistic targets of antifungal agents: an overview, *Mini Rev. Med. Chem.* 16 (2016) 555–578, <https://doi.org/10.2174/1389557516666160118112103>.
- [11] A. Abd Rashed, D.-N.G. Rathi, N.A.H. Ahmad Nasir, A.Z. Abd Rahman, Antifungal properties of essential oils and their compounds for application in skin fungal infections: conventional and nonconventional approaches, *Molecules* 26 (2021) 1093, <https://doi.org/10.3390/molecules26041093>.
- [12] A.H. Fairlamb, N.A.R. Gow, K.R. Matthews, A.P. Waters, Drug resistance in eukaryotic microorganisms, *Nat. Microbiol.* 1 (2016), 16092, <https://doi.org/10.1038/nmicrobiol.2016.92>.
- [13] C.N. Powers, J.L. Osier, R.L. McFeeters, C.B. Brazell, E.L. Olsen, D.M. Moriarity, P. Satyal, W.N. Setzer, Antifungal and cytotoxic activities of sixty commercially-available essential oils, *Molecules* 23 (2018) 1549, <https://doi.org/10.3390/molecules23071549>.
- [14] A. Mutlu-Ingok, D. Devecioglu, D.N. Dikmetas, F. Karbancioglu-Guler, E. Capanoglu, Antibacterial, antifungal, antimycotoxigenic, and antioxidant activities of essential oils: an updated review, *Molecules* 25 (2020) 4711, <https://doi.org/10.3390/molecules25204711>.
- [15] F. Laffleur, V. Keckeis, Advances in drug delivery systems: work in progress still needed? *Int. J. Pharm. X.* 2 (2020), 100050 <https://doi.org/10.1016/j.ijpx.2020.100050>.
- [16] P. Reginatto, V.Z. Bergamo, S.J. Berlitz, I.C.K. Guerreiro, S.F. de Andrade, A. M. Fuentefria, Rational selection of antifungal drugs to propose a new formulation strategy to control *Candida* biofilm formation on venous catheters, *Braz. J. Microbiol.* 51 (2020) 1037–1049, <https://doi.org/10.1007/s42770-020-00242-z>.
- [17] C. Mota Fernandes, D. Dasilva, K. Haranahalli, J.B. McCarthy, J. Mallamo, I. Ojima, M. Del Poeta, The future of antifungal drug therapy: novel compounds and targets, *Antimicrob. Agents Chemother.* 65 (2021) e01719–e01720, <https://doi.org/10.1128/AAC.01719-20>.
- [18] R. Abonia, A. Garay, J.C. Castillo, B. Insuasty, J. Quiroga, M. Noguera, J. Cobo, E. Butassi, S. Zacchino, Design of two alternative routes for the synthesis of naptifine and analogues as potential antifungal agents, *Molecules* 23 (2018) 520, <https://doi.org/10.3390/molecules23030520>.
- [19] M.A. Ghannoum, L.B. Rice, Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance, *Clin. Microbiol. Rev.* 12 (1999) 501–517, <https://doi.org/10.1128/CMR.12.4.501>.
- [20] E.L. Berkow, S.R. Lockhart, L. Ostrosky-Zeichner, Antifungal susceptibility testing: current approaches, *Clin. Microbiol. Rev.* 33 (2020), <https://doi.org/10.1128/CMR.00069-19> e00069-19.
- [21] J.A. Parente-Rocha, A.M. Bailão, A.C. Amaral, C.P. Taborda, J.D. Paccez, C. L. Borges, M. Pereira, Antifungal resistance, metabolic routes as drug targets, and new antifungal agents: an overview about endemic dimorphic fungi, *Mediat. Inflamm.* (2017), 9870679, <https://doi.org/10.1155/2017/9870679>, 2017.
- [22] M.A. Pfaller, Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment, *Am. J. Med.* 125 (2012), <https://doi.org/10.1016/j.amjmed.2011.11.001> S3–13.
- [23] M. Sanguinetti, B. Posteraro, C. Lass-Flörl, Antifungal drug resistance among *Candida* species: mechanisms and clinical impact, *Mycoses* 58 (Suppl 2) (2015) 2–13, <https://doi.org/10.1111/myc.12330>.
- [24] J. Berman, D.J. Krysan, Drug resistance and tolerance in fungi, *Nat. Rev. Microbiol.* 18 (2020) 319–331, <https://doi.org/10.1038/s41579-019-0322-2>.
- [25] K.E. Pristov, M.A. Ghannoum, Resistance of *Candida* to azoles and echinocandins worldwide, *Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis.* 25 (2019) 792–798, <https://doi.org/10.1016/j.cmi.2019.03.028>.

- [26] R.K. Shields, M.H. Nguyen, C.J. Clancy, Clinical perspectives on echinocandin resistance among *Candida* species, *Curr. Opin. Infect. Dis.* 28 (2015) 514–522, <https://doi.org/10.1097/QCO.0000000000000215>.
- [27] D.S. Perlin, Echinocandin resistance, susceptibility testing and prophylaxis: implications for patient management, *Drugs* 74 (2014) 1573–1585, <https://doi.org/10.1007/s40265-014-0286-5>.
- [28] C.M. Hull, O. Bader, J.E. Parker, M. Weig, U. Gross, A.G.S. Warrillow, D.E. Kelly, S.L. Kelly, Two clinical isolates of *Candida glabrata* exhibiting reduced sensitivity to amphotericin B both harbor mutations in ERG2, *Antimicrob. Agents Chemother.* 56 (2012) 6417–6421, <https://doi.org/10.1128/AAC.01145-12>.
- [29] S. Ahmad, L. Joseph, J.E. Parker, M. Asadzadeh, S.L. Kelly, J.F. Meis, Z. Khan, ERG6 and ERG2 are major targets conferring reduced susceptibility to amphotericin B in clinical *Candida glabrata* isolates in Kuwait, *Antimicrob. Agents Chemother.* 63 (2019), <https://doi.org/10.1128/AAC.01900-18>.
- [30] H. Carolus, S. Pierson, K. Lagrou, P. Van Dijk, Amphotericin B and other polyene-discovery, clinical use, mode of action and drug resistance, *J. Fungi (Basel, Switzerland)* 6 (2020) 321, <https://doi.org/10.3390/jof6040321>.
- [31] P. Lakhani, A. Patil, S. Majumdar, Challenges in the polyene- and azole-based pharmacotherapy of ocular fungal infections, *J. Ocul. Pharmacol. Ther. Off. J. Assoc. Ocul. Pharmacol. Ther.* 35 (2019) 6–22, <https://doi.org/10.1089/jop.2018.0089>.
- [32] B. Wilson, G. Abraham, V.S. Manju, M. Mathew, B. Vimala, S. Sundaresan, B. Nambisan, Antimicrobial activity of *Curcuma zedoaria* and *Curcuma malabarica* tubers, *J. Ethnopharmacol.* 99 (2005) 147–151, <https://doi.org/10.1016/j.jep.2005.02.004>.
- [33] H. Khan, M.S. Mubarak, S. Amin, Antifungal potential of alkaloids as an emerging therapeutic target, *Curr. Drug Targets* 18 (2017) 1825–1835, <https://doi.org/10.2174/1389450117666160719095517>.
- [34] A. Kumar, F. Khan, D. Saikia, Exploration of medicinal plants as sources of novel anticandidal drugs, *Curr. Top. Med. Chem.* 19 (2019) 2579–2592, <https://doi.org/10.2174/1568026619666191025155856>.
- [35] T. Arif, J.D. Bhosale, N. Kumar, T.K. Mandal, R.S. Bendre, G.S. Lavekar, R. Dabur, Natural products–antifungal agents derived from plants, *J. Asian Nat. Prod. Res.* 11 (2009) 621–638, <https://doi.org/10.1080/10286020902942350>.
- [36] Q. Liu, W. Luyten, K. Pellens, Y. Wang, W. Wang, K. Thevissen, Q. Liang, B.P. A. Cammue, L. Schoofs, G. Luo, Antifungal activity in plants from Chinese traditional and folk medicine, *J. Ethnopharmacol.* 143 (2012) 772–778, <https://doi.org/10.1016/j.jep.2012.06.019>.
- [37] M.A.B. Rajeh, Z. Zuraini, S. Sasidharan, L.Y. Latha, S. Amutha, Assessment of *Euphorbia hirta* L. leaf, flower, stem and root extracts for their antibacterial and antifungal activity and brine shrimp lethality, *Molecules* 15 (2010) 6008–6018, <https://doi.org/10.3390/molecules15096008>.
- [38] N.B. Bottari, L.Q.S. Lopes, K. Pizzuti, C. Filippi Dos Santos Alves, M.S. Corrêa, L. P. Bolzan, A. Zago, R. de Almeida Vaucher, A.A. Boligon, J.L. Giongo, M. D. Baldissera, R.C.V. Santos, Antimicrobial activity and phytochemical characterization of *Carya illinoensis*, *Microb. Pathog.* 104 (2017) 190–195, <https://doi.org/10.1016/j.micpath.2017.01.037>.
- [39] C. de Andrade Monteiro, J.R.A. dos Santos, Phytochemicals and their antifungal potential against pathogenic yeasts, in: V. Rao, D. Mans, L. Rao (Eds.), *Phytochem. Hum. Heal., IntechOpen, Rijeka*, 2020, <https://doi.org/10.5772/intechopen.87302>.
- [40] S.B. Waller, M.B. Cleff, E.F. Serra, A.L. Silva, A.D.R. Gomes, J.R.B. de Mello, R. O. de Faria, M.C.A. Meireles, Plants from Lamiaceae family as source of antifungal molecules in humane and veterinary medicine, *Microb. Pathog.* 104 (2017) 232–237, <https://doi.org/10.1016/j.micpath.2017.01.050>.
- [41] B. Barros Cota, D. Batista Carneiro de Oliveira, T. Carla Borges, A. Cristina Catto, C. Valverde Serafim, A. Rogelis Aquiles Rodrigues, M. Kohlhoff, C. Leomar Zani, A. Assunção Andrade, Antifungal activity of extracts and purified saponins from the rhizomes of *Chamaecostus cuspidatus* against *Candida* and *Trichophyton* species, *J. Appl. Microbiol.* 130 (2021) 61–75, <https://doi.org/10.1111/jam.14783>.
- [42] A.G. Terças, A. de S. Monteiro, E.B. Moffa, J.R.A. Dos Santos, E.M. de Sousa, A.R. B. Pinto, P.C. da S. Costa, A.C.R. Borges, L.M.B. Torres, A.K.D. Barros Filho, E. S. Fernandes, C. de A. Monteiro, Phytochemical characterization of *Terminalia catappa* linn. Extracts and their antifungal activities against *Candida* spp, *Front. Microbiol.* 8 (2017) 595, <https://doi.org/10.3389/fmicb.2017.00595>.
- [43] S. Akroum, Antifungal activity of acetone extracts from *Punica granatum* L., *Quercus suber* L. and *Vicia faba* L., *J. Mycol. Med.* 27 (2017) 83–89, <https://doi.org/10.1016/j.mycmed.2016.10.004>.
- [44] V. Todorovic, M. Milenkovic, B. Vidovic, Z. Todorovic, S. Sobajic, Correlation between antimicrobial, antioxidant activity, and polyphenols of alkalinized/nonalkalized cocoa powders, *J. Food Sci.* 82 (2017) 1020–1027, <https://doi.org/10.1111/1750-3841.13672>.
- [45] R.M. Plant, L. Dinh, S. Argo, M. Shah, The essentials of essential oils, *Adv. Pediatr.* 66 (2019) 111–122, <https://doi.org/10.1016/j.yapd.2019.03.005>.
- [46] A. Elaissi, Z. Rouis, N.A. Ben Salem, S. Mabrouk, Y. ben Salem, K.B.H. Salah, M. Aouni, F. Farhat, R. Chemli, F. Harzallah-Skhiri, M.L. Khouja, Chemical composition of 8 eucalyptus species' essential oils and the evaluation of their antibacterial, antifungal and antiviral activities, *BMC Compl. Alternative Med.* 12 (2012) 81, <https://doi.org/10.1186/1472-6882-12-81>.
- [47] S. Tariq, S. Wani, W. Rasool, K. Shafi, M.A. Bhat, A. Prabhakar, A.H. Shalla, M. A. Rather, A comprehensive review of the antibacterial, antifungal and antiviral potential of essential oils and their chemical constituents against drug-resistant microbial pathogens, *Microb. Pathog.* 134 (2019), 103580, <https://doi.org/10.1016/j.micpath.2019.103580>.
- [48] K. Uma, X. Huang, B.A. Kumar, Antifungal effect of plant extract and essential oil, *Chin. J. Integr. Med.* 23 (2017) 233–239, <https://doi.org/10.1007/s11655-016-2524-z>.
- [49] D. Kalembe, A. Kunicka, Antibacterial and antifungal properties of essential oils, *Curr. Med. Chem.* 10 (2003) 813–829, <https://doi.org/10.2174/0929867033457719>.
- [50] H. Tolba, H. Moghrani, A. Benelmouffok, D. Kellou, R. Maachi, Essential oil of Algerian *Eucalyptus citriodora*: chemical composition, antifungal activity, *J. Mycol. Med.* 25 (2015) e128–e133, <https://doi.org/10.1016/j.mycmed.2015.10.009>.
- [51] N. da Silva Bomfim, C.Y. Kohiyama, L.P. Nakasugi, S.B. Nerilo, S.A.G. Mossini, J. C.Z. Romoli, J.M. Graton Mikcha, B.A. de Abreu Filho, M.J. Machinski, Antifungal and antiaflatoxinogenic activity of rosemary essential oil (*Rosmarinus officinalis* L.) against *Aspergillus flavus*, *Food Addit. Contam. Part A, Chem. Anal. Control. Expo. Risk Assess.* 37 (2020) 153–161, <https://doi.org/10.1080/19440049.2019.1678771>.
- [52] A. Maccioni, D. Falconieri, S. Porcedda, A. Piras, M.J. Gonçalves, J.M. Alves-Silva, L. Salgueiro, A. Maxia, Antifungal activity and chemical composition of the essential oil from the aerial parts of two new *Teucrium capitatum* L. chemotypes from Sardinia Island, Italy., *Nat. Prod. Res.* 35 (2021) 6007–6013, <https://doi.org/10.1080/14786419.2020.1813136>.
- [53] G. Ghasemi, A. Alirezalu, S.R. Ishkeh, Y. Ghosta, Phytochemical properties of essential oil from *Artemisia sieberi* Besser (Iranian accession) and its antioxidant and antifungal activities, *Nat. Prod. Res.* 35 (2021) 4154–4158, <https://doi.org/10.1080/14786419.2020.1741576>.
- [54] K.K.A. Santos, E.F.F. Matias, S.R. Tintino, C.E.S. Souza, M.F.B.M. Braga, G.M. M. Guedes, J.G.M. Costa, I.R.A. Menezes, H.D.M. Coutinho, Enhancement of the antifungal activity of antimicrobial drugs by *Eugenia uniflora* L., *J. Med. Food* 16 (2013) 669–671, <https://doi.org/10.1089/jmf.2012.0245>.
- [55] K. Jassal, S. Kaushal, R. Rani Rashmi, Antifungal potential of guava (*Psidium guajava*) leaves essential oil, major compounds: beta-caryophyllene and caryophyllene oxide, *Arch. Phytopathol. Plant Protect.* 54 (2021) 2034–2050, <https://doi.org/10.1080/03235408.2021.1968287>.
- [56] C. Chen, L. Long, F. Zhang, Q. Chen, C. Chen, X. Yu, Q. Liu, J. Bao, Z. Long, Antifungal activity, main active components and mechanism of *Curcuma longa* extract against *Fusarium graminearum*, *PLoS One* 13 (2018), e0194284, <https://doi.org/10.1371/journal.pone.0194284>.
- [57] D. Savarirajan, V.M. Ramesh, A. Muthaiyan, In vitro antidermatophytic activity of bioactive compounds from selected medicinal plants, *J. Anal. Sci. Technol.* 12 (2021) 53, <https://doi.org/10.1186/s40543-021-00304-3>.
- [58] K.A. de M. Torres, S.M.R.R. Lima, S.M.Y. Ueda, Activity of the aqueous extract of *Schinus terebinthifolius* Raddi on strains of the *Candida* genus, *Rev. Bras. Ginecol. e Obstet. Rev. Da Fed. Bras. Das Soc. Ginecol. e Obstet.* 38 (2016) 593–599, <https://doi.org/10.1055/s-0036-1597694>.
- [59] J.J.G. Leite, E.H.S. Brito, R.A. Cordeiro, R.S.N. Brilhante, J.J.C. Sidrim, L. M. Bertini, S.M. de Moraes, M.F.G. Rocha, Chemical composition, toxicity and larvicidal and antifungal activities of *Persea americana* (avocado) seed extracts, *Rev. Soc. Bras. Med. Trop.* 42 (2009) 110–113, <https://doi.org/10.1590/s0037-86822009000200003>.
- [60] D.A. Sampietro, A. de L.A. Gomez, C.M. Jimenez, E.F. Lizarraga, Z.A. Ibatayev, Y. M. Suleimen, C.A. Catalán, Chemical composition and antifungal activity of essential oils from medicinal plants of Kazakhstan, *Nat. Prod. Res.* 31 (2017) 1464–1467, <https://doi.org/10.1080/14786419.2016.1258560>.
- [61] E. de Souza Araújo, A.S. Pimenta, F.M.C. Feijó, R.V.O. Castro, M. Fasciotti, T.V. C. Monteiro, K.M.G. de Lima, Antibacterial and antifungal activities of pyrolytic acid from wood of *Eucalyptus urograndis* and *Mimosa tenuiflora*, *J. Appl. Microbiol.* 124 (2018) 85–96, <https://doi.org/10.1111/jam.13626>.
- [62] M. Yemele Bouberte, K. Krohn, H. Hussain, E. Dongo, B. Schulz, Q. Hu, Tithoniamarin and tithoniamide: a structurally unique isocoumarin dimer and a new ceramide from *Tithonia diversifolia*, *Nat. Prod. Res.* 20 (2006) 842–849, <https://doi.org/10.1080/14786410500462892>.
- [63] A. Portillo, R. Vila, B. Freixa, E. Ferro, T. Parella, J. Casanova, S. Cañigueral, Antifungal sesquiterpene from the root of *Vernonanthura Tweediana*, *J. Ethnopharmacol.* 97 (2005) 49–52, <https://doi.org/10.1016/j.jep.2004.09.052>.
- [64] J.C. Castro, G.C. Pante, B.M. Centenaro, R.T.R. De Almeida, E.J. Pilau, B.P. Dias Filho, S.A.G. Mossini, B.A. De Abreu Filho, G. Matioli, M. Machinski Junior, Antifungal and antimycotoxinogenic effects of *Zingiber officinale*, *Cinnamomum zeylanicum* and *Cymbopogon martinii* essential oils against *Fusarium verticillioides*, *Food Addit. Contam. Part A, Chem. Anal. Control. Expo. Risk Assess.* 37 (2020) 1531–1541, <https://doi.org/10.1080/19440049.2020.1778183>.
- [65] S. Bawazeer, A. Rauf, Vitro antibacterial and antifungal potential of amyrin-type triterpenoid isolated from *Datura metel* Linnaeus, *BioMed Res. Int.* (2021), 1543574, <https://doi.org/10.1155/2021/1543574>, 2021.
- [66] Y.-M. Kim, C.-H. Lee, H.-G. Kim, H.-S. Lee, Anthraquinones isolated from *Cassia tora* (Leguminosae) seed show an antifungal property against phytopathogenic fungi, *J. Agric. Food Chem.* 52 (2004) 6096–6100, <https://doi.org/10.1021/jf049379p>.
- [67] N.T. Manojlovic, S. Solujic, S. Sukdolak, M. Milosevic, Antifungal activity of *Rubia tinctorum*, *Rhamnus frangula* and *Caloplaca cerina*, *Fitoterapia* 76 (2005) 244–246, <https://doi.org/10.1016/j.fitote.2004.12.002>.
- [68] T.H. Kang, E.-I. Hwang, B.S. Yun, C.S. Shin, S.U. Kim, Chitin synthase 2 inhibitory activity of O-methyl pisiferic acid and 8,20-dihydroxy-9(11),13-abetadien-12-one, isolated from *Chamaecyparis pisifera*, *Biol. Pharm. Bull.* 31 (2008) 755–759, <https://doi.org/10.1248/bpb.31.755>.

- [69] K.K. Mishra, C.D. Kaur, A.K. Sahu, R. Panik, P. Kashyap, S.P. Mishra, S. Dutta, Medicinal plants having antifungal properties, in: B.A.R. Hassan (Ed.), *Med. Plants*, IntechOpen, Rijeka, 2020, <https://doi.org/10.5772/intechopen.90674>.
- [70] A.M. do Nascimento, M.J. Salvador, R.C. Candido, S. de Albuquerque, D.C.R. de Oliveira, Trypanocidal and antifungal activities of p-hydroxyacetophenone derivatives from *Calea uniflora* (Heliantheae, Asteraceae), *J. Pharm. Pharmacol.* 56 (2004) 663–669, <https://doi.org/10.1211/0022357023231>.
- [71] W. Xu, J. Li, D. Li, J. Tan, H. Ma, Y. Mu, Y. Wen, L. Gan, X. Huang, L. Li, Chemical characterization, antiproliferative and antifungal activities of *Clinacanthus nutans*, *Fitoterapia* 155 (2021), 105061, <https://doi.org/10.1016/j.fitote.2021.105061>.
- [72] E. Butassi, L.A. Svetaz, S. Zhou, J.-L. Wolfender, J.C.G. Cortés, J.C. Ribas, C. Díaz, J.P.-D. Palacio, F. Vicente, A.S. Zacchino, The antifungal activity and mechanisms of action of quantified extracts from berries, leaves and roots of *Phytolacca tetramera*, *Phytomedicine* 60 (2019), 152884, <https://doi.org/10.1016/j.phymed.2019.152884>.
- [73] B.R. Meena, S. Meena, D. Chittora, K. Sharma, Antifungal efficacy of *Thevetia peruviana* leaf extract against *Alternaria solani* and characterization of novel inhibitory compounds by Gas Chromatography-Mass Spectrometry analysis, *Biochem. Biophys. Reports* 25 (2021), 100914, <https://doi.org/10.1016/j.bbrep.2021.100914>.
- [74] G. Simonetti, E. Brasili, G. Pasqua, Antifungal activity of phenolic and polyphenolic compounds from different matrices of *Vitis vinifera* L. Against human pathogens, *Molecules* 25 (2020), <https://doi.org/10.3390/molecules25163748>.
- [75] X. Da, Y. Nishiyama, D. Tie, K.Z. Hein, O. Yamamoto, E. Morita, Antifungal activity and mechanism of action of *Ou-gon* (*Scutellaria* root extract) components against pathogenic fungi, *Sci. Rep.* 9 (2019) 1683, <https://doi.org/10.1038/s41598-019-38916-w>.
- [76] X. Li, X. Wang, C. Li, M. Khutsishvili, G. Fayvush, D. Atha, Y. Zhang, R.P. Borris, Unusual flavones from *Primula macrocalyx* as inhibitors of OAT1 and OAT3 and as antifungal agents against *Candida rugosa*, *Sci. Rep.* 9 (2019) 9230, <https://doi.org/10.1038/s41598-019-45728-5>.
- [77] B. Armendáriz-Barragán, N. Zafar, W. Badri, S.A. Galindo-Rodríguez, D. Kabbaj, H. Fessi, A. Elaissari, Plant extracts: from encapsulation to application, *Expet Opin. Drug Deliv.* 13 (2016) 1165–1175, <https://doi.org/10.1080/17425247.2016.1182487>.
- [78] R. Tirkey, A. Deepkujur, K. Yadav, V. Tripathi, D. Dewangan, S. Saraf, Potential of neoteric phytoactives and herbs for targeting pathophysiological modules of arthritis, *Bull. Environ. Pharmacol. Life Sci.* 10 (2021) 273–281.
- [79] K. Yadav, M.R. Singh, V.K. Rai, N. Srivastava, N. Prasad Yadav, Commercial aspects and market potential of novel delivery systems for bioactives and biological agents, in: *Adv. Ave. Dev. Nov. Carriers Bioact. Biol. Agents*, Elsevier, 2020, pp. 595–620, <https://doi.org/10.1016/b978-0-12-819666-3.00020-1>.
- [80] K. Yadav, N.S. Chauhan, S. Saraf, D. Singh, M.R. Singh, Challenges and need of delivery carriers for bioactives and biological agents: an introduction, in: *Adv. Ave. Dev. Nov. Carriers Bioact. Biol. Agents*, Elsevier, 2020, pp. 1–36, <https://doi.org/10.1016/b978-0-12-819666-3.00001-8>.
- [81] K. Yadav, J. Pawar, D. Singh, M.R. Singh, Promising phytoactives candidates for efficacious treatment of psoriasis and other skin disorders, *J. Ravishankar Univ.* 31 (2019) 10–22, <https://doi.org/10.52228/jrub.2018-31-1-2>.
- [82] M. Ekor, The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety, *Front. Pharmacol.* 4 (2014) 177, <https://doi.org/10.3389/fphar.2013.00177>.
- [83] H.S. Rahman, H.H. Othman, N.I. Hammadi, S.K. Yeap, K.M. Amin, N. Abdul Samad, N.B. Alitheen, Novel drug delivery systems for loading of natural plant extracts and their biomedical applications, *Int. J. Nanomed.* 15 (2020) 2439–2483, <https://doi.org/10.2147/IJN.S227805>.
- [84] V.K. Devi, N. Jain, K.S. Valli, Importance of novel drug delivery systems in herbal medicines, *Pharmacogn. Rev.* 4 (2010) 27–31, <https://doi.org/10.4103/0973-7847.65322>.
- [85] R. Pandey, M. Bhairam, S.S. Shukla, B. Gidwani, Colloidal and vesicular delivery system for herbal bioactive constituents, *Daru* 29 (2021) 415–438, <https://doi.org/10.1007/s40199-021-00403-x>.
- [86] K. Yadav, D. Singh, M.R. Singh, Nanovesicles delivery approach for targeting steroid mediated mechanism of antipsoriatic therapeutics, *J. Drug Deliv. Sci. Technol.* 65 (2021), 102688, <https://doi.org/10.1016/j.jddst.2021.102688>.
- [87] K. Yadav, D. Singh, M.R. Singh, M. Pradhan, Multifaceted targeting of cationic liposomes via co-delivery of anti-IL-17 siRNA and corticosteroid for topical treatment of psoriasis, *Med. Hypotheses* 145 (2020), 110322, <https://doi.org/10.1016/j.mehy.2020.110322>.
- [88] M.A. Jahangir, C. Anand, A. Muheem, S.J. Gilani, M. Taleuzzaman, A. Zafar, M. Jafar, S. Verma, M.A. Barkat, Nano phytomedicine based delivery system for CNS disease, *Curr. Drug Metabol.* 21 (2020) 661–673, <https://doi.org/10.2174/1389200221666200523161003>.
- [89] H.M. Ahmed, S. Nabavi, S. Behzad, Herbal drugs and natural products in the light of nanotechnology and nanomedicine for developing drug formulations, *Mini Rev. Med. Chem.* 21 (2021) 302–313, <https://doi.org/10.2174/1389557520666200916143240>.
- [90] V. Dave, S. Sharma, R.B. Yadav, U. Agarwal, Herbal liposome for the topical delivery of ketoconazole for the effective treatment of seborrheic dermatitis, *Appl. Nanosci.* 7 (2017) 973–987, <https://doi.org/10.1007/s13204-017-0634-3>.
- [91] A. Mittal, N. Kumar, N.S. Chauhan, Curcumin encapsulated PEGylated nanoliposomes: a potential anti-infective therapeutic agent, *Indian J. Microbiol.* 59 (2019) 336–343, <https://doi.org/10.1007/s12088-019-00811-3>.
- [92] Y. Zhao, Y.-X. Chang, X. Hu, C.-Y. Liu, L.-H. Quan, Y.-H. Liao, Solid lipid nanoparticles for sustained pulmonary delivery of Yuxingcao essential oil: preparation, characterization and in vivo evaluation, *Int. J. Pharm.* 516 (2017) 364–371, <https://doi.org/10.1016/j.ijpharm.2016.11.046>.
- [93] N. Feng, J.-H. Zhao, Y. Liu, Z. Wang, Y.-T. Zhang, N.-P. Feng, Preparation and characterization of solid lipid nanoparticles loaded with frankincense and myrrh oil, *Int. J. Nanomed.* 7 (2012) 2033, <https://doi.org/10.2147/IJN.S30085>.
- [94] K. Yadav, D. Singh, M.R. Singh, Development and characterization of corticosteroid loaded lipid carrier system for psoriasis, *Res. J. Pharm. Technol.* 14 (2021) 966–970, <https://doi.org/10.5958/0974-360X.2021.00172.4>.
- [95] T.L.C. Lima, L.B.F.C. Souza, L.C.S. Tavares-Pessoa, A.M. Dos Santos-Silva, R. S. Cavalcante, R.F. de Araújo-Júnior, A.M. Cornélio, M.F. Fernandes-Pedrosa, G. M. Chaves, A.A. da Silva-Júnior, Phytol-loaded solid lipid nanoparticles as a novel anticandidal nanobiotechnological approach, *Pharmaceutics* 12 (2020), <https://doi.org/10.3390/pharmaceutics12090871>.
- [96] C.-Y. Shen, L. Dai, B.-D. Shen, X. Zhou, J.-X. Bai, H. Xu, Q.-Y. Lv, J. Han, H.-L. Yuan, Nanostructured lipid carrier based topical gel of Ganoderma Triterpenoids for frostbite treatment, *Chin. J. Nat. Med.* 13 (2015) 454–460, [https://doi.org/10.1016/S1875-5364\(15\)30039-X](https://doi.org/10.1016/S1875-5364(15)30039-X).
- [97] M. Pradhan, A. Alexander, M.R. Singh, D. Singh, S. Saraf, S. Saraf, K. Yadav, Ajazuddin, Statistically optimized calcipotriol fused nanostructured lipid carriers for effectual topical treatment of psoriasis, *J. Drug Deliv. Sci. Technol.* 61 (2021), 102168, <https://doi.org/10.1016/j.jddst.2020.102168>.
- [98] M. Pradhan, K. Yadav, D. Singh, M.R. Singh, Topical delivery of fluocinolone acetonide integrated NLCs and salicylic acid enriched gel: a potential and synergistic approach in the management of psoriasis, *J. Drug Deliv. Sci. Technol.* 61 (2021), 102282, <https://doi.org/10.1016/j.jddst.2020.102282>.
- [99] I. Lacatusu, D. Istrati, M. Popescu, A.M. Seciu, L.M. Panteli, N. Badea, Synergism of plant extract and vegetable oils-based lipid nanocarriers: emerging trends in development of advanced cosmetic prototype products, *Mater. Sci. Eng. C. Mater. Biol. Appl.* 108 (2020), 110412, <https://doi.org/10.1016/j.msec.2019.110412>.
- [100] K. Yadav, D. Singh, M.R. Singh, Novel archetype in psoriasis management bridging molecular dynamics in exploring novel therapies, *Eur. J. Pharmacol.* 907 (2021), 174254, <https://doi.org/10.1016/j.ejphar.2021.174254>.
- [101] M.R. Singh, D. Singh, K.K. Sahu, M.Y. Pradhan Krishna, A Method of Preparation of Triamcinolone Acetonide Encapsulated Nanostructured Lipid Carriers for Psoriasis Treatment, 2021.
- [102] I. Baldim, L. Tonani, M.R. von Zeska Kress, W. Pereira Oliveira, Lippia sidoides essential oil encapsulated in lipid nanosystem as an anti-Candida agent, *Ind. Crop. Prod.* 127 (2019) 73–81, <https://doi.org/10.1016/j.indcrop.2018.10.064>.
- [103] M.K. Bhalari, S. Naik, A.N. Misra, Ethosomes: a novel delivery system for antifungal drugs in the treatment of topical fungal diseases, *Indian J. Exp. Biol.* 47 (2009) 368–375.
- [104] S. Shetty, J. Jose, L. Kumar, R.N. Charyulu, Novel ethosomal gel of clove oil for the treatment of cutaneous candidiasis, *J. Cosmet. Dermatol.* 18 (2019) 862–869, <https://doi.org/10.1111/jocd.12765>.
- [105] Y. Singh, J.G. Meher, K. Raval, F.A. Khan, M. Chaurasia, N.K. Jain, M. K. Chourasia, Nanoemulsion: concepts, development and applications in drug delivery, *J. Contr. Release* 252 (2017) 28–49, <https://doi.org/10.1016/j.jconrel.2017.03.008>.
- [106] S. Das, B. Horváth, S. Šafranko, S. Jokić, A. Széchenyi, T. Kőszegi, Antimicrobial activity of chamomile essential oil: effect of different formulations, *Molecules* 24 (2019), <https://doi.org/10.3390/molecules24234321>.
- [107] R. Mahajan, R. Tandon, A. Kalia, B.V.C. Mahajan, Nanoemulsion formulation of *Ocimum gratissimum* essential oil and its antifungal activity against *Penicillium digitatum*, *J. Nanosci. Nanotechnol.* 21 (2021) 3556–3565, <https://doi.org/10.1166/jnn.2021.19008>.
- [108] A.K. Kammoon, A. Khedr, M.A. Hegazy, A.J. Almalki, K.M. Hosny, W. A. Abualsunun, S.S.A. Murshid, R.B. Bakhaider, Formulation, optimization, and nephrotoxicity evaluation of an antifungal in situ nasal gel loaded with voriconazole–clove oil transferosomal nanoparticles, *Drug Deliv.* 28 (2021) 2229–2240, <https://doi.org/10.1080/10717544.2021.1992040>.
- [109] T. Vangijzegem, D. Stanicki, S. Laurent, Magnetic iron oxide nanoparticles for drug delivery: applications and characteristics, *Expet Opin. Drug Deliv.* 16 (2019) 69–78, <https://doi.org/10.1080/17425247.2019.1554647>.
- [110] K. Yadav, M. Pradhan, D. Singh, M.R. Singh, in: N. Rezaei (Ed.), *Targeting Autoimmune Disorders through Metal Nanoformulation in Overcoming the Fences of Conventional Treatment Approaches*, *Transl. Autoimmun., Academic Press*, 2022, pp. 361–393, <https://doi.org/10.1016/b978-0-12-824390-9.00017-7>.
- [111] M. Mohammadi, S.A. Shahisaraee, A. Tavajjohi, N. Pourmoori, S. Muhammadnejad, S.R. Mohammadi, R. Poursalehi, H. Delavari H, Green synthesis of silver nanoparticles using *Zingiber officinale* and *Thymus vulgaris* extracts: characterisation, cell cytotoxicity, and its antifungal activity against *Candida albicans* in comparison to fluconazole, *IET Nanobiotechnol.* 13 (2019) 114–119, <https://doi.org/10.1049/iet-nbt.2018.5146>.
- [112] D.H. Nguyen, J.S. Lee, K.D. Park, Y.C. Ching, X.T. Nguyen, V.H.G. Phan, T. T. Hoang Thi, Green silver nanoparticles formed by *Phyllanthus urinaria*, *Pouzolzia zeylanica*, and *Scoparia dulcis* leaf extracts and the antifungal activity, *Nanomaterials* (2020) 10, <https://doi.org/10.3390/nano10030542>.
- [113] S. Paul, K. Mohanram, I. Kannan, Antifungal activity of curcumin-silver nanoparticles against fluconazole-resistant clinical isolates of *Candida* species, *Ayu* 39 (2018) 182–186, <https://doi.org/10.4103/ayu.AYU.24.18>.
- [114] M. Karkhane, H.E. Lashgarian, S.Z. Mirzaei, A. Ghaffarizadeh, K. cherghipour, A. Sepahvand, A. Marzban, Antifungal, antioxidant and photocatalytic activities

- of zinc nanoparticles synthesized by *Sargassum vulgare* extract, *Biocatal. Agric. Biotechnol.* 29 (2020), 101791, <https://doi.org/10.1016/j.bcab.2020.101791>.
- [115] K. Yadav, A. Soni, D. Singh, M.R. Singh, Polymers in topical delivery of anti-psoriatic medications and other topical agents in overcoming the barriers of conventional treatment strategies, *Prog. Biomater.* 10 (2021) 1–17, <https://doi.org/10.1007/s40204-021-00154-7>.
- [116] M. Izadi, S.A. Moosawi Jorf, M. Nikkhhah, S. Moradi, Antifungal activity of hydrocolloid nano encapsulated *Carum copticum* essential oil and *Peganum harmala* extract on the pathogenic fungi *Alternaria alternata*, *Physiol. Mol. Plant Pathol.* 116 (2021), 101714, <https://doi.org/10.1016/j.pmpp.2021.101714>.
- [117] I. Muzzalupo, G. Badolati, A. Chiappetta, N. Picci, R. Muzzalupo, In vitro antifungal activity of olive (*olea europaea*) leaf extracts loaded in chitosan nanoparticles, *Front. Bioeng. Biotechnol.* 8 (2020) 151, <https://doi.org/10.3389/fbioe.2020.00151>.
- [118] T. Suwan, S. Khongkhunthian, S. Okonogi, Antifungal activity of polymeric micelles of silver nanoparticles prepared from *Psidium guajava* aqueous extract, *Drug Discov. Ther.* 13 (2019) 62–69, <https://doi.org/10.5582/ddt.2019.01024>.
- [119] C.M.B. Pinilla, R.C.S. Thys, A. Brandelli, Antifungal properties of phosphatidylcholine-oleic acid liposomes encapsulating garlic against environmental fungal in wheat bread, *Int. J. Food Microbiol.* 293 (2019) 72–78, <https://doi.org/10.1016/j.ijfoodmicro.2019.01.006>.
- [120] C.F. Bezerra, J.G. de A. Júnior, R. de L. Honorato, A.T.L. dos Santos, J.C.P. da Silva, T.G. da Silva, T.S. de Freitas, T.A.T. Vieira, M.C.F. Bezerra, D. Lima Sales, J. P. V Rodrigues, J.M.B. Filho, L.R. Peixoto, A.P. Pinheiro, H.D.M. Coutinho, M.F. B. Morais-Braga, T.G. da Silva, Antifungal effect of liposomal α -bisabolol and when associated with fluconazole, *Cosmet* 8 (2021), <https://doi.org/10.3390/cosmetics8020028>.
- [121] E. Moghimipour, N. Aghel, A.Z. Mahmoudabadi, Z. Ramezani, S. Handali, Preparation and characterization of liposomes containing essential oil of *Eucalyptus camaldulensis* leaf, *Jundishapur J. Nat. Pharm. Prod.* 7 (2012) 117–122, <https://doi.org/10.5812/jjnpp.5261>.
- [122] L. Risaliti, G. Pini, R. Ascrizzi, R. Donato, C. Sacco, M.C. Bergonzi, M.C. Salvatici, A.R. Bilia, *Artemisia annua* essential oil extraction, characterization, and incorporation in nanoliposomes, smart drug delivery systems against *Candida* species, *J. Drug Deliv. Sci. Technol.* 59 (2020), 101849, <https://doi.org/10.1016/j.jddst.2020.101849>.
- [123] M. Nasserli, S. Golmohammadzadeh, H. Arouiee, M.R. Jaafari, H. Neamati, Antifungal activity of *Zataria multiflora* essential oil-loaded solid lipid nanoparticles in-vitro condition, *Iran, J. Basic Med. Sci.* 19 (2016) 1231–1237, <https://pubmed.ncbi.nlm.nih.gov/27917280>.
- [124] G. Svetlichny, I.C. Küllkamp-Guerreiro, S.L. Cunha, F.E.K. Silva, K. Bueno, A. R. Pohlmann, A.M. Fuentefria, S.S. Guterres, Solid lipid nanoparticles containing copaiba oil and allantoin: development and role of nanoencapsulation on the antifungal activity, *Pharmazie* 70 (2015) 155–164.
- [125] P. Essential, D.T. Uchida, G.F. Siqueira, E. Marques, L. Hegeto, A.M. Neto, A. V. Reis, M.L. Bruschi, V. Nova, M. Machinski, *Design of Nanostructured Lipid Carriers Containing*, 2021.
- [126] M. Radi, H. Ahmadi, S. Amiri, Effect of cinnamon essential oil-loaded nanostructured lipid carriers (NLC) against *penicillium citrinum* and *penicillium expansum* involved in tangerine decay, *Food Bioprocess Technol.* 15 (2022) 306–318, <https://doi.org/10.1007/s11947-021-02737-5>.
- [127] S.B. Jaffri, K.S. Ahmad, Augmented photocatalytic, antibacterial and antifungal activity of prunosynthetic silver nanoparticles, *Artif. Cell Nanomed. Biotechnol.* 46 (2018) 127–137, <https://doi.org/10.1080/21691401.2017.1414826>.
- [128] M. Singh, M. Kumar, R. Kalaivani, S. Manikandan, A.K. Kumaraguru, Metallic silver nanoparticle: a therapeutic agent in combination with antifungal drug against human fungal pathogen, *Bioproc. Biosyst. Eng.* 36 (2013) 407–415, <https://doi.org/10.1007/s00449-012-0797-y>.
- [129] A. Gupta, S.R. Bonde, S. Gaikwad, A. Ingle, A.K. Gade, M. Rai, Lawsonia inermis-mediated synthesis of silver nanoparticles: activity against human pathogenic fungi and bacteria with special reference to formulation of an antimicrobial nanogel, *IET Nanobiotechnol.* 8 (2014) 172–178, <https://doi.org/10.1049/iet-nbt.2013.0015>.
- [130] S. Valsalam, P. Agastian, M.V. Arasu, N.A. Al-Dhabi, A.-K.M. Ghilan, K. Kaviyarasu, B. Ravindran, S.W. Chang, S. Arokiyaraj, Rapid biosynthesis and characterization of silver nanoparticles from the leaf extract of *Tropaeolum majus* L. and its enhanced in-vitro antibacterial, antifungal, antioxidant and anticancer properties, *J. Photochem. Photobiol., B* 191 (2019) 65–74, <https://doi.org/10.1016/j.jphotobiol.2018.12.010>.
- [131] M.A. Asghar, E. Zahir, S.M. Shahid, M.N. Khan, M.A. Asghar, J. Iqbal, G. Walker, Iron, copper and silver nanoparticles: green synthesis using green and black tea leaves extracts and evaluation of antibacterial, antifungal and aflatoxin B1 adsorption activity, *LWT* 90 (2018) 98–107, <https://doi.org/10.1016/j.lwt.2017.12.009>.
- [132] W. Wang, R. Zhu, Q. Xie, A. Li, Y. Xiao, K. Li, H. Liu, D. Cui, Y. Chen, S. Wang, Enhanced bioavailability and efficiency of curcumin for the treatment of asthma by its formulation in solid lipid nanoparticles, *Int. J. Nanomed.* 7 (2012) 3667–3677, <https://doi.org/10.2147/IJN.S30428>.