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Carbon Nanotube Hybrid Materials: Efficient and Pertinent Platforms for Antifungal Drug Delivery

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Carbon nanotubes (CNTs) have emerged as the brightest nascent artifact to deliver antifungal drugs in drug delivery applications, health care, and pharmaceutical industries. Excellent physio-chemical features such as huge surface area, tunable side wall, and microneedle-like morphology make CNTs suitable for drug carriers. Chemical attachments (covalent and non-covalent functionalization) result in the formation of functionalized CNTs (F-CNTs) and CNT-based hybrid materials (CNT-HMs). These F-CNTs and CNT-HMs have substantial antifungal activity and also have the potential to immobilize antifungal drugs such as amphotericin B, nystatin, curcumin, etc. on the exterior or interior surface, securely transport to the target sites, permeate through bio-barriers, and release these drugs in a controlled manner. As antifungal drug carriers, F-CNT and CNT-HMs exhibit more excellent antifungal activity than other conventional drug delivery systems and have the potency to invade biofilm to circumvent the multidrug resistance of fungal species. This review focuses on CNTs and CNT-HMs for antifungal drug delivery, including their functionalization methods, drug loading approaches, drug release mechanism, cellular internalization, delivery efficiency, and cellular toxicities with their workaround.

1. Introduction

Aside from the emergence of multidrug resistance, the number of patients at risk for invasive fungal infections has increased significantly in the last decade.[1] These infectious fungal species cause human disease termed mycosis, which can be either primary or opportunistic. The site of infection in the host's body can be categorized into four classes: superficial, cutaneous, subcutaneous, and invasive fungal infections. Among these, invasive fungal infection has been the most prevalent and severe cause of diseases and deaths globally. Numerically, pathogenic fungi such as *Candida*, *Aspergillus*, and *Cryptococcus* cause more than 1 million devastating invasive fungal infections yearly.[1] Candidiasis, aspergillosis, and cryptococcosis invasive fungal infections affect over 0.7 million, 0.3 million, and 0.2 million people yearly.[2,3] These fungal infections typically occur in immunocompromised patients subjected to other infectious microbes such as viruses, bacteria, and parasitic protozoans.[4] Currently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a causative agent of Coronavirus disease 2019 (COVID-19),[5] has been spread to more than 256 countries or territories and declared a pandemic by WHO on March 11, 2020,[6,7] The COVID-19 pandemic has been managed chiefly with supportive care, respiratory failure prevention (such as mechanical ventilation), antiviral medication (such as corticosteroid treatment, dysbiosis antibiotics, TNF-α antagonistic drugs, renin-angiotensin-aldosterone system inhibitors), and immunization (such as vaccination). These immunosuppressive procedures boost the number of immunocompromised patients more vulnerable to microbial co- and superinfections.[8,12] These immunocompromised COVID-19 patients have been diagnosed with viral infections (such as entero- or rhinovirus, human metapneumovirus, and respiratory syncytial virus), bacterial infections (such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces*), and fungal infections (such as *Aspergillus* spp., *Candidaalbicans*, and *Candidaglabrata*).[9,10] Candidiasis has been investigated as the most common mycosis, and *C. albicans* has been ranked as the fourth most common causative organism of nosocomial infections (Candidiasis) globally.[11–13] Although currently, available antifungal drugs such as polyenes, azoles, allylamines, echinocandins, and antimetabolites have been helpful in many circumstances, they suffer from a confluence of systemic toxicities (such as hydrophobicity, poor pharmacokinetics, and -dynamics, low bioavailability, systemic side

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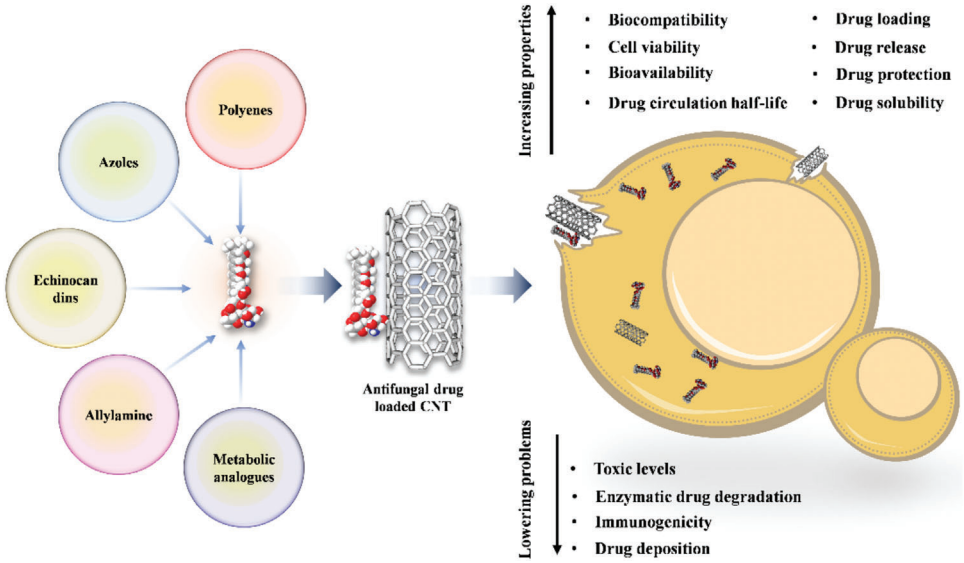

Figure 1. Illustrative image of the characteristics of carbon nanotube hybrid-based antifungal drug delivery systems; (the authors designed the images by using ChemDraw Pro 8.0 (PerkinElmer) and Microsoft PowerPoint).

effects) and escalating resistance that hinders their therapeutic efficiency.[14] These limitations of existing antifungal drugs have been overcome by formulation methods of novel antifungal drugs,[14] improvements of existing antifungal drugs,[14] combination therapy,[14] and efficient delivery approaches for antifungal drugs.

Numerous micro- to nano-sized antifungal drug delivery systems (AF-DDS) have been developed, including conventional and modern approaches. However, traditional methods like polymer, lipid, and nanoparticle-based AF-DDS suffer from drug load and cell membrane penetration limitations. Modern AF-DDS are being pursued to address these issues, with carbon nanotubes (CNTs) emerging as efficient candidates.[15,16] Their exceptional physical (large surface area,[7] conductivity,[7,16] mechanical strength,[16]) chemical (homogeneous atomic composition, tunable sidewalls), and antimicrobial properties[7] have spurred intense research. Functionalization enables the binding of CNTs to various functional groups, which are used to link other valuable molecules, thus forming CNT-based hybrid materials (CNT-HMs).[16,17] Coupling these hybrids (inorganic, organic) through various approaches enhances CNT properties, which are relevant for biomedical applications like drug delivery, cancer therapy, and antimicrobial use.[16,18,19] CNTs possess antimicrobial activity against various microorganisms such as viruses,[7,20] bacteria,[7,20] fungi,[7,20] and other parasitic organisms, while CNT-HMs can synergistically enhance this activity. Functionalized CNTs (F-CNTs; hydrophilic-CNTs,[21] carboxylated-CNTs[21]) and CNT-HMs exhibit inhibition of the growth of biofilms in a dose-and strain-dependent manner.[22] Their abilities to permeate cell membranes, extended circulation, enhanced solubility, and biocompatibility make them promising AF-DDS candidates[16,23] (**Figure 1**). The lack of scholarly literature on CNTs and CNT-HMs as AF-DDS is evident across diverse scientific databases, substantially hampering research endeavors. This comprehensive review investigates the potential utility of CNTs and CNT-HMs in AF-DDS, encompassing fungal taxonomy, pathogenicity, antifungal agents, drug delivery modalities, CNT properties, synthesis, and applications.

2. Fungal Infections, Antifungal Drugs, and Delivery System

≈70 000 of the estimated 5 000 000 fungal species have been identified on the earth and divided into nine phyla; Chytridiomycota, Opisthosporidia, Neocallimastigomycota, Blastocladiomycota, Zoopagomycota, Mucoromycota, Glomerulomycota, Ascomycota, and Basidiomycota. The Basidiomycota and Ascomycota have been the most researched phyla, and only the Ascomycota phylum has the most species. Fungi are usually dimorphic, with filamentous (multicellular hyphae) and unicellular forms. Their cell wall and extracellular matrix comprise complex polysaccharides such as mannans, Galatians, glucans, and chitin, which have been antifungal drug target sites. The majority of ailments in both plants and animals have been attributed to pathogenic fungi such as *Candida* spp., *Aspergillus* spp., and *Cryptococcus* spp.[24] Most human mycosis has been caused by unicellular and filamentous fungi, classified based on the site of infections into four classes such as superficial, cutaneous, subcutaneous, and invasive. Superficial and cutaneous mycosis develops in the outer dermal layer (stratum corneum), and the integument includes skin, hair, and nails. Subcutaneous mycosis affects the subcutaneous tissues, whereas invasive mycosis affects deeper tissues such as the respiratory, circulatory, gastrointestinal, neurological, and endocrine systems. Invasive mycosis has impacted humankind strongly, with high mortality (95%) caused by opportunistic fungi.[25]

2.1. Devastating Fungal Infections for Human

Human mycosis has been a significant concern on a global scale, becoming a serious global health problem with catastrophic

socioeconomic consequences in addition to high morbidity and mortality rates. Immune-modulating drugs and excessive antibiotics used in transplant patients boost the at-risk population, particularly those prone to mycosis, including older adults and severely unwell or immunocompromised patients. This is a significant factor in increasing the number of mycoses. The eye, oropharynx, genital tract, and skin are the standard routes of entry of pathogenic fungal species into the human body. They are transmitted through the bloodstream up to various parts of the body. These pathogens have been localized and colonized at different layers of the tissues at the site of infection. These common routes of entry, translocation mechanisms, and invasion sites are illustrated in **Figure 2**.

Although ≈1.5 million people die yearly due to fungal infections (predominantly associated with *Candida*, *Cryptococcus*, and *Aspergillus* species), modern researchers routinely disregard fungus pathogenicity.[3,26–28] Thousands of instances of mucormycosis (predominantly caused by *Mucor*, *Apophysomyces*, *Lichtheimia*, and *Rhizopus* species) have recently been identified, most in India among 18 countries throughout the COVID-19 second wave, boosting awareness of this lethal but ignored infection.[28,29] Mycobiota and polymycobiota conditions have been linked to morbidities and co-morbidities, which can alter immunity and make the patient immunocompromised.[30] Despite the prevalence and lethality of mycosis, the mycology field has been underfunded in recent decades compared to other infections, such as bacterial, viral, and parasitic, for diagnostic and therapeutic research.[28] Manufacturing novel antifungal drugs has been daunting since fungi are more evolutionarily similar to humans than other harmful species.[3,31]

2.2. Antifungal Drugs and Their Resistance Mechanism

Many synthetic and natural antifungal drugs have been developed to treat mycoses. These can be fungistatic (hinder fungal growth only) and fungicidal (kill the fungal cell), and based on chemical structure classified into five main classes: polyenes (amphotericin B; AMB and nystatin; NYS), azoles (econazole; ECZ, miconazole; MIZ, croconazole; CCZ, ketoconazole; KTZ, fluconazole; FLC, itraconazole; ITZ, voriconazole; VRC), allylamines (terbinafine; TRB, naftifine; NF, and Butenafine), echinocandins (caspofungin; CAS, micafungin; MCF, and anidulafungin; AFG), and antimetabolites, whereas other antifungals include ciclopirox (CPX), griseofulvin (GF), and amorolfine.[3,32] Polyenes and azoles were clinically approved in the 1980s, while echinocandins were developed and authorized in the 20th century. Popular antifungal drugs for aspergillosis included AMB, VRC, posaconazole, ITZ, MCF, CAS, AFG, FLC, KTZ, ITZ, polygodial, AMB, MIZ, and pyraclostrobin used for candidiasis. In contrast, pyraclostrobin, AMB, ITZ, ITZ, and FLC are used for cryptococcosis.

However, these antifungal drugs are extensively prescribed for treating invasive and superficial mycosis. The development of resistance against them is the primary cause of worldwide concern, particularly in patients with immunocompromised diseases arising from the endemic, epidemic, and pandemic infection waves faced periodically in life.[31] Microbial antifungal drug resistance is classified as intrinsic (primary), acquired (secondary), and clinical resistance. The number, level, and mechanism of resistance exhibited by common fungal species against antifungal drugs are illustrated in **Figure 3**.

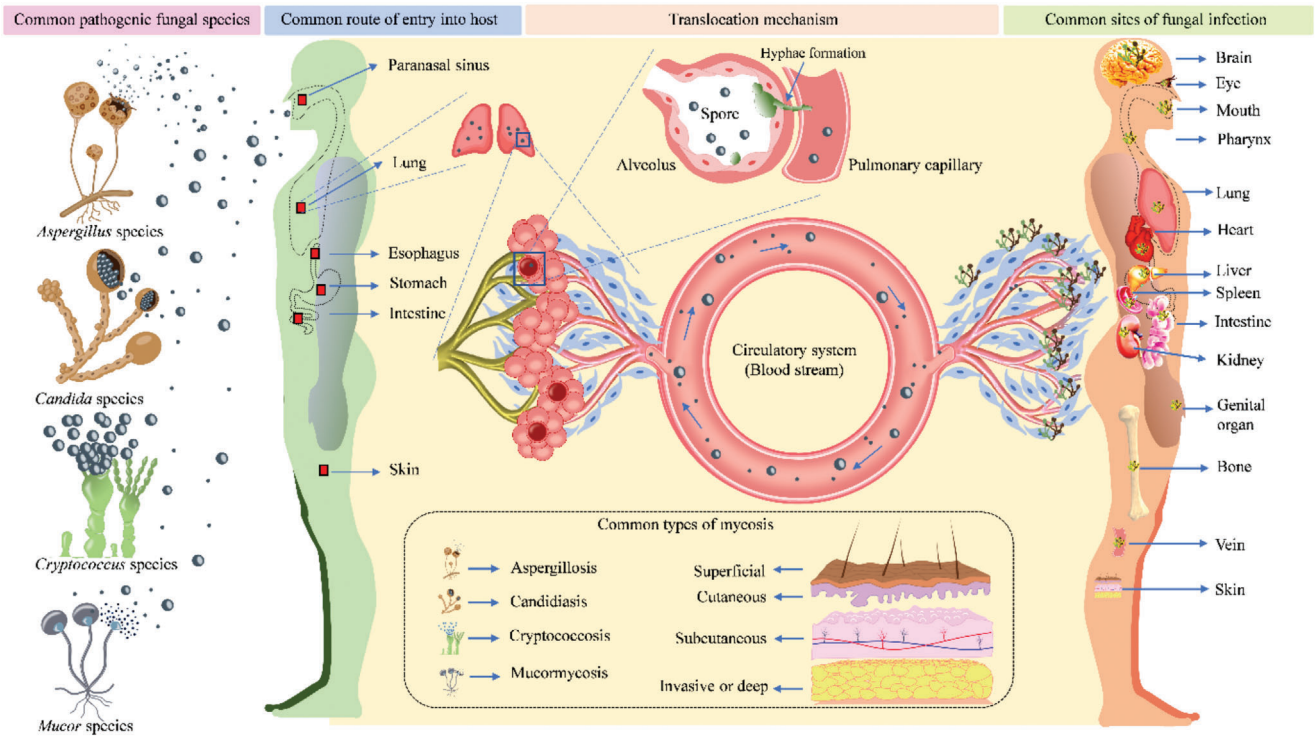

Figure 2. Schematic illustration of common pathogenic fungal species, route of entry, translocation mechanism, and common sites of infection in the human body; (the authors designed the images by using ChemDraw Pro 8.0 (PerkinElmer) and Microsoft PowerPoint).

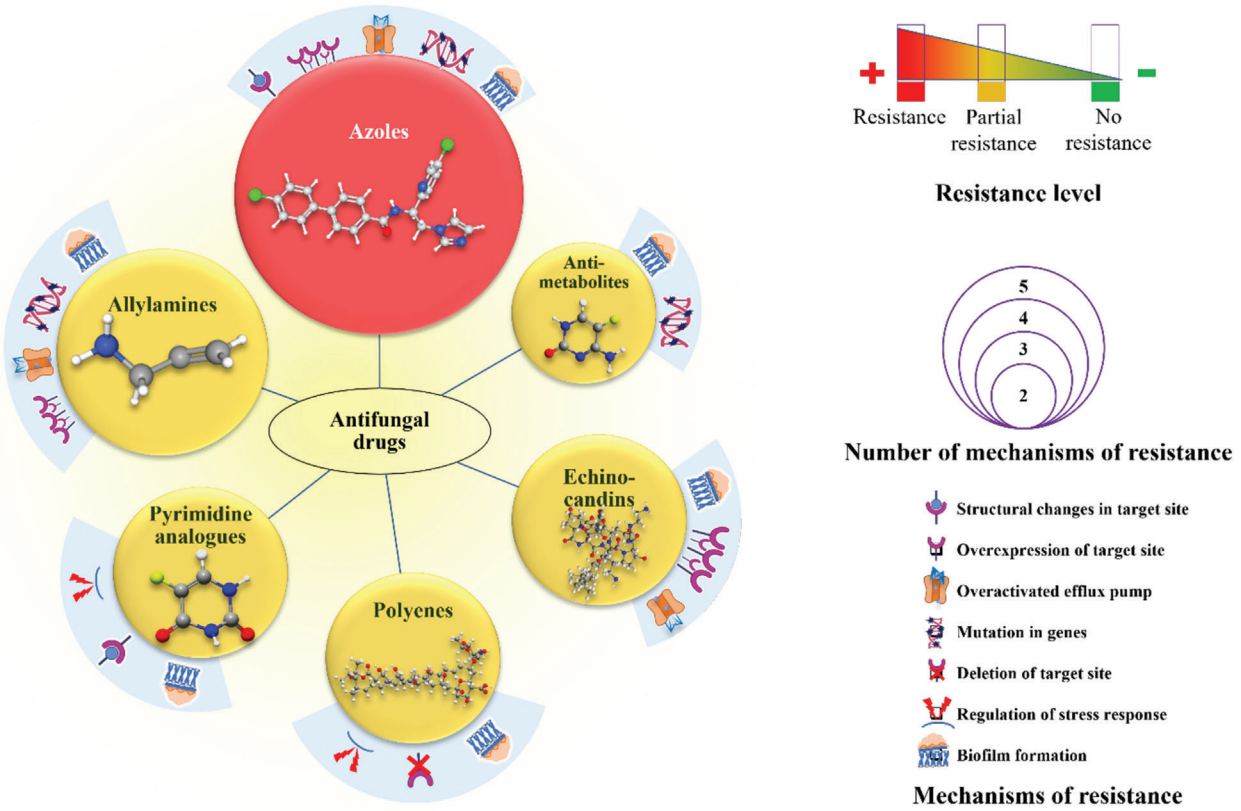

Figure 3. Diagrammatic illustration portraying the existing antifungal agents and documented levels of resistance mechanisms within fungal cells; (the authors designed the images by using ChemDraw Pro 8.0 (PerkinElmer) and Microsoft PowerPoint).

Genetic and natural factors are involved in intrinsic resistance, whereas long-term, repeated, and prophylactically administration of antifungal drugs can be involved in the evolution of acquired resistance, and clinical resistance is detected in patients with prolonged, profound immunological deficiencies or contaminated prosthetic equipment.[33,34] *Candida* and *Aspergillus* species significantly manifest resistance against Azole and Polyenes antifungals, whereas *Cryptococcus* species are substantially resistant to echinocandin and azole antifungals. *Cryptococcus* has hetero-resistance (due to additional chromosomal copies that have efflux pump AFR1 and ERG11) and can multiply, albeit at eight times the concentration of antifungal drugs. There is a widespread problem since the development of antifungals is outpacing the expansion of resistance of pathogenic fungi. The molecular mechanism of resistance by a fungal cell is illustrated in **Figure 4**.

Resistance to existing antifungal drugs is increasing exponentially and is challenging to treat. These limitations need the development of innovative antifungal drugs and high-efficiency delivery systems to succeed in eradication. Most of the antifungal medicines have systemic side effects, low bioavailability,[35] toxic nature by self,[35] low water solubility, variability in absorption, and poor clinical efficiency due to their limitations regarding pharmacokinetics, pharmacodynamics, the spectrum of antifungal activity, harmful drug-drug interactions,[35] reduced efficacy by the mechanism of resistance,[35] toxicity profile, and physicochemical characteristic phylogenetic similarity between humans and fungi. To overcome these limitations of antifungal drugs, scientists/doctors for antifungal treatment are investigating newer opportunities, including the search for new antifungal drugs and alternate mechanisms of delivery.[35] Nanoformulations for antifungal drug delivery provide enhanced therapeutic and prolonged effects with broad-spectrum antifungal activity.

3. Conventional and Modern AF-DDS

The drug used to treat, diagnose, prevent, or mitigate disease is termed the drug according to the FDA, and techniques used to deliver drugs into the body of patients to increase efficiency and efficacy are called a DDS. The physical state of the drugs, such as solid (tablets, powder, aerosol, plaster), semisolid gels (ointments, cream, paste), suspensions, and solutions (syrups), altered the route of delivery of the drugs, which played a decisive role in the formulation of novel antifungal drugs as well their delivery system.[37] Antifungal drugs are delivered via several techniques with many routes, a few of which are in use today but have undergone adaptations, as illustrated in **Figure 5**.

Many researchers have reported a wide range of AF-DDS, including liposomes (LIP), niosomes, proniosomes, transferosomes, ethosomes, transethosomes, bilosomes, cubosomes, spanlastics, cerosomes, terpesomes, novasomes,

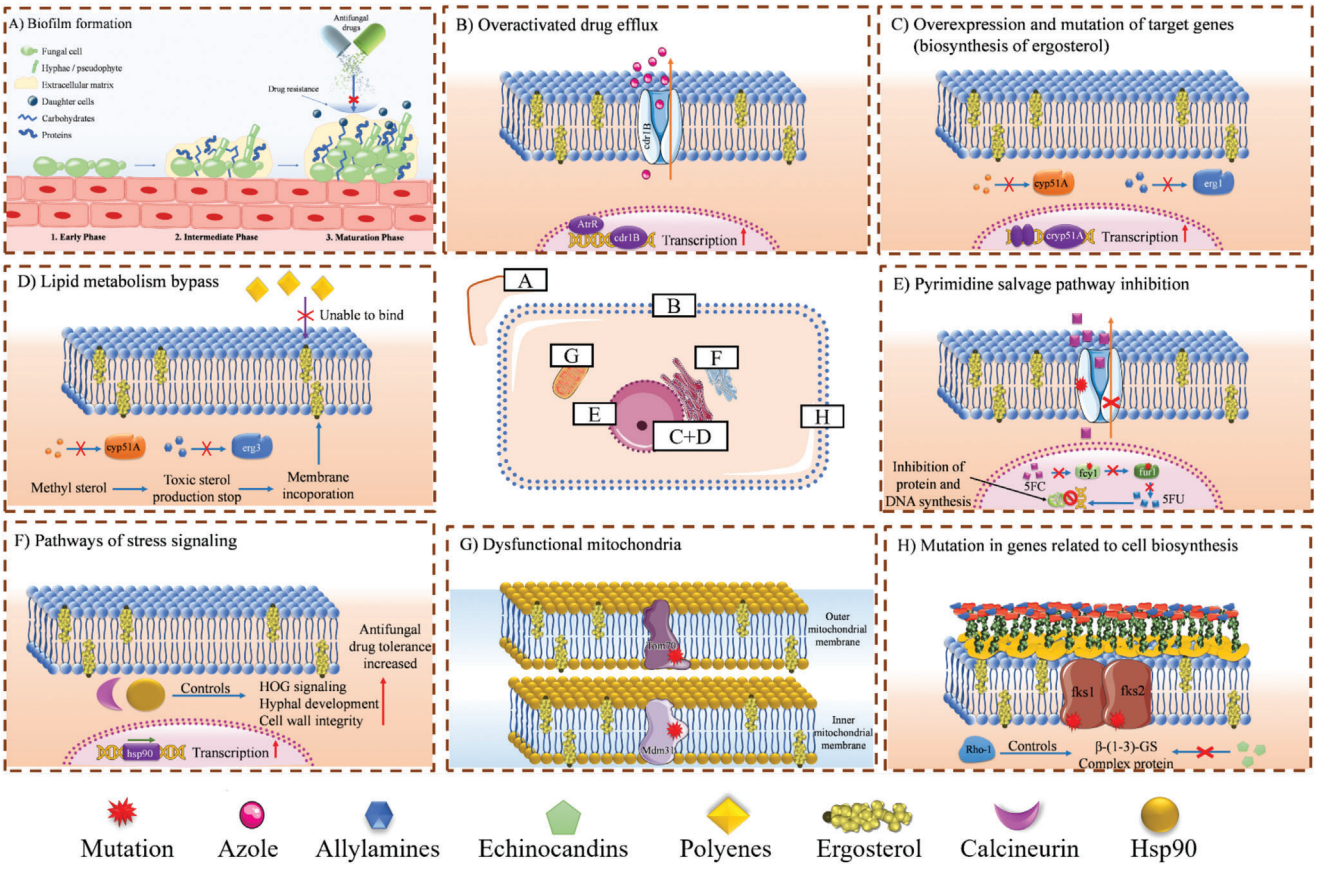

Figure 4. Predominant resistance mechanism exhibited by fungal cells against established antifungal agents. Reproduced with permission.[36] Copyright 2019, Elsevier.

polymerosomes, oleic acid vesicles, lipid micelles, and dendrimers[32,39] (**Figure 6**). These systems deliver drugs like AMB, MIZ, ECZ, KTZ, clotrimazole (CTZ), ITZ, FLC, TRB, NYS, CCZ, tolnaftate, AGF, CPX, VRC, terconazole, natamycin, luliconazole, fenticonazole nitrate, CAS, MCF, 5-Fluorouracil (5-FU), Isavuconazole (ISA) etc. through routes such as intravenous, topical, and more.[3,15,32,35,40–56] Their antifungal activities have been investigated against a diverse range of fungal species like *Candida albicans, Candida tropicalis, Aspergillus flavus, Aspergillus niger, Cryptococcus tropicum, Trichophyton rubrum, Microsporum canis, Aspergillus nidulans, Microsporum gypseum, Microsporum canis, Trichophyton mentagrophytes, Saccharomyces cerevisiae*, and others[3,15,32,35,40–56] (**Table 1**).

Diverse drug modification techniques, like functional groups and chemical conjugation, have enhanced drug delivery. These approaches are applied across various DDSs for antifungal drugs, such as injectables, patches, capsules, and nanoparticles.[32,39] Effective DDSs with high loading capacity, extended retention time, metabolic stability, and controlled drug release mitigate nephrotoxicity and enhance patient compliance. Nanocarriers (NCs) hold promise in meeting these criteria and represent a contemporary drug delivery approach. Many NCs were used to deliver antifungal drugs, including solid lipid NPs, nanostructured lipid carriers, and polymeric NPs (**Figure 7 and Table 2**).

Reportedly, conventional DDSshave many disadvantages[18,23] such as circulating half-life is short,[32,60] less target specificity,[61] adverse effects,[62] inadequate efficiency,[62] drug deposition at target area,[61–63] low pharmacokinetic properties,[62] toxicity,[63] low water solubility,[63] low bioavailability,[32,60,61] variation in plasma drug level,[61] leakage of drug,[32,41] difficulties in scale-up,[41] dose dumping,[41] sterilization problems,[41] poor yielding,[41] chances of coalescence,[41] expensive.[41] Advanced nanomaterials such as CNTs offer a promising solution to address abovementioned limitations of conventional DDSs due to higher drug loading capacity (high aspect ratio),[18,23] controlled drug release,[18] competence to penetrate across plasma membranes (nanoneedle shape),[18,23] flexibility in surface modification (functionalization), lower to higher molecular sized drugs can be encapsulated,[18] protection of the drug from cytosolic enzyme degradation (encapsulation in core space),[23] thermal ablation.[18]

4. A Brief Overview of CNTs

The Discovery of CNTs (1991 by Sumio Iijima) ignited global scientific fascination. CNTs are an allotropic carbon macromolecule in which sp^2 hybridized carbon atoms are hexagonally organized (referred to as a graphene sheet) and cylindrically rolled (termed a nanotube), yielding exceptional nanostructures with a high length-to-diameter ratio.[64] Synthesis methods of CNTs broadly fall into three categories: chemical, physical, and other approaches. Chemical processes involve oxidizing graphite

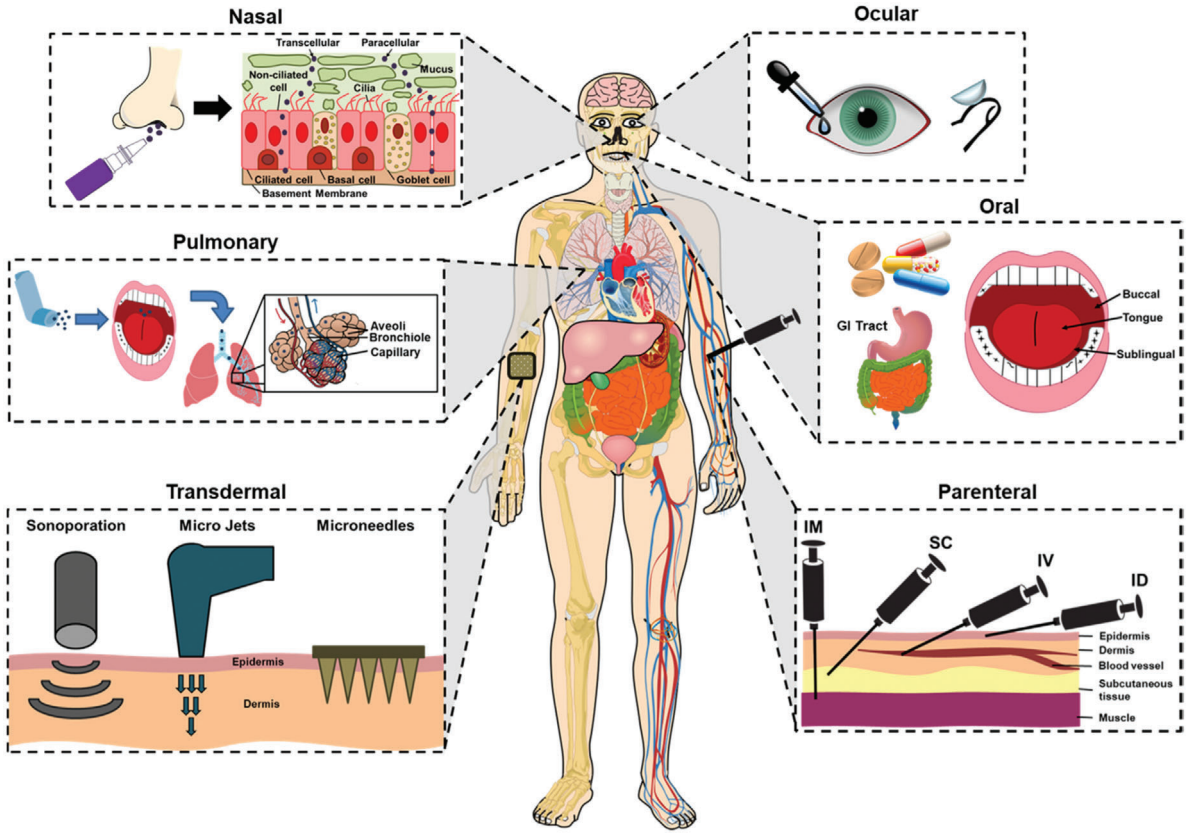

Figure 5. Illustration of various drug delivery systems employed to deliver antifungal drugs and their route of administration. Reproduced with permission.[38] Copyright 2020, Elsevier.

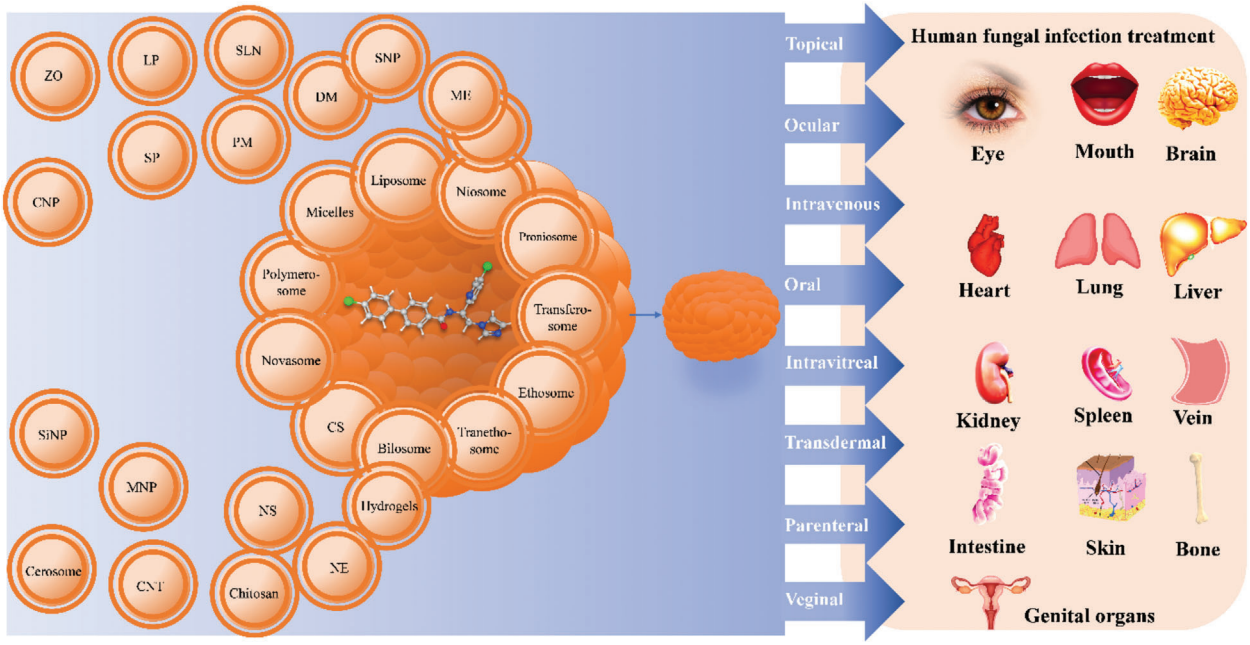

Figure 6. Schematic illustration of their role as antifungal nanocarriers, route of administration, and their uses for treating various fungal infections in humans. Cubosome, CS; Carbon nanotube, CNT; Nanoemulsion, NE; Nanosponges, NS; Silver nanoparticle, SiNP; Silica nanoparticle, SNP; Dendrimers, DM; Zinc oxide, ZO; Spanlastics, SP; Polymeric micelles, PM; Copper nanoaparticels, CNP; Microemulsion, ME; Solid lipid nanoparticle, SLN; Magnetic nanoparticles, MNP. (the authors designed the images by using ChemDraw Pro 8.0 (PerkinElmer) and Microsoft PowerPoint).

Table 1. Lipid-based antifungal drug delivery system.

Delivery system	Delivered antifungal drugs	Major components	Route of administration	Fungal species	Refs.
Liposome	AMB, MIZ, ECZ, KTZ, CTZ, ITZ, FLC, TRB, NYS, CCZ, TOL, TRB, AFG, curcumin	Phosphatidylcholine, cholesterol, di-stearoyl phosphatidyl-glycerol, Span 80, Soya Lecithin.	Intravenous, topical, intravitral	*Candida* spp.; *C. albicans*, *C. tropicalis*, *Aspergillus* spp.; *A. flavus*, *A. niger*, *Cryptococcal* spp.; *C. tropicum*, *Trichophyton* spp.; *T. rubrum*, *Penicillium* spp.; *P. chrysogenum*	[3,15,35,40,41]
Niosomes	MIZ, ECZ, KTZ, CTZ, ITZ, FLC, NF, NYS, GF, CPX	Phosphatidylcholine, cholesterol, distearoyl phosphatidylethanolamine, Span 80, Span 40, Span 60, Tween 60, ethanol	Transdermal, topical, ocular, parenteral, oral	*Candida* spp.;*C. albicans*, *Aspergillus* spp.; *A. niger*	[3,41]
Proniosomes	ITZ, VRC CPX CTZ AMB	Cholesterol, Span 60, lecithin	Transdermal, ocular, topical	*Candida* spp.;*C. albicans*, *Aspergillus* spp.; *A. nidulans*	[3,32,42–44]
Transferosomes	MIZ, AMB, CTZ, ITZ, TRB, VRC, GF	Phosphatidylcholine, phospholipid, sodium deoxycholate,Tween-80, Span-60, Span-80, cholesterol, phospholipon 90 G, ethanol	Topical, transdermal	*Candida* spp.;*C. albicans*, *Aspergillus* spp.;*A. flavus*, *Microsporum* spp.;*M. gypseum*,*M. canis*, *Trichophyton* spp.;*T. mentagrophytes*, *T. rubrum*	[3,32,41,45]
Ethosomes	CPX, AMB, ECZ, FLC, VRC, CTZ	Soya phosphatidylcholine, lipoid S PC-3, ethanol, soya lecithin, cavamax, propylene glycol	Transdermal, topical	*Candida* spp.;*C. albicans*, *Aspergillus* spp.;*A. flavus*,*A. niger*	[3,32,35,41]
Transethosomes	VRC, KTZ, ECZ,	Lipoid S100, various edge activators, L-A-phosphatidylcholine, Tween 80, Span 80, stearyl amine, ethanol, propylene glycol,	Topical, ocular, transdermal	*Candida* spp.;*C. albicans*	[3,32,41,46]
Bilosomes	TCZ, NAT	Cholesterol, Span 60, bile salts, edge activators, sodium taurocholate, cremophor, ethanol	Topical, ocular	*Candida* spp.;*C. albicans*	[32,47]
Cubosomes	NYS, VRC	Glycerol monooleate, various surfactants, monoolein & Pluronic F1, phytantriol	Inhalable, ocular	*Aspergillus* spp.; *A. flavus*	[32,48]
Spanlastics	CTZ, LCZ, MIZ, ITZ, FLC, TRB, KTZ,	Span 60, Span 65, Span 20, Tween 20, Tween 80, sodium deoxycholate, Pluronic F1	Ocular, topical, transungual	*Candida* spp.; *C. albican*	[3,32,41,49,50]
Cerosomes	FTN	Ceramide phospholipid, different types of Brij	Topical		[32,51]
Terpesomes	FTN	Sodium deoxycholate, terpenes, phospholipids,	Vaginal ocular	*Candida* spp.; *C. albicans*	[32,52]
Novasomes	TCZ, FTN	Cholesterol, Span 60, Span 80, oleic acid, stearic acid, Brij		*Candida* spp.; *C. albicans*	[32,53,54]
Polymerosome	AMB, ITZ	Oleic acid, methanol	Intravenous, oral		[3,32,41]
Oleic acid vesicle	FLC, CTZ	Oleic acid	Topical	*Candida* spp.; *C. albicans*	[41]
Lipid micelles	AMB	Sodium deoxycholate	Intravenous	*Candida* spp.; *C. albicans*, *C. neoformans*,*Saccharomyces* spp.; *S. cerevisiae*	[3,55,56]
Dendrimers	AMB, KTZ	Polyamidoamine	Topical		[3,35]

AMB, Amphotericin B; MIZ, Miconazole; ECZ, Econazole; KTZ, Ketoconazole; CTZ, Clotrimazole; ITZ, Itraconazole; FLC, Fluconazole; TRB, Terbinafine; NYS, Nystatin; CCZ, Croconazole; TOL, Tolnaftate; AFG, Anidulafungin; NF, Naftifine; GF, Griseofulvin; CPX, Ciclopirox; VRC, Voriconazole; TCZ, Terconazole; NAT, Natamycin; LCZ, Luliconazole; FTN, Fenticonazole nitrate; CAS, Caspofungin; MCF, Micafungin; 5-FU, 5-Fluorouracil; ISA, Isavuconazole.

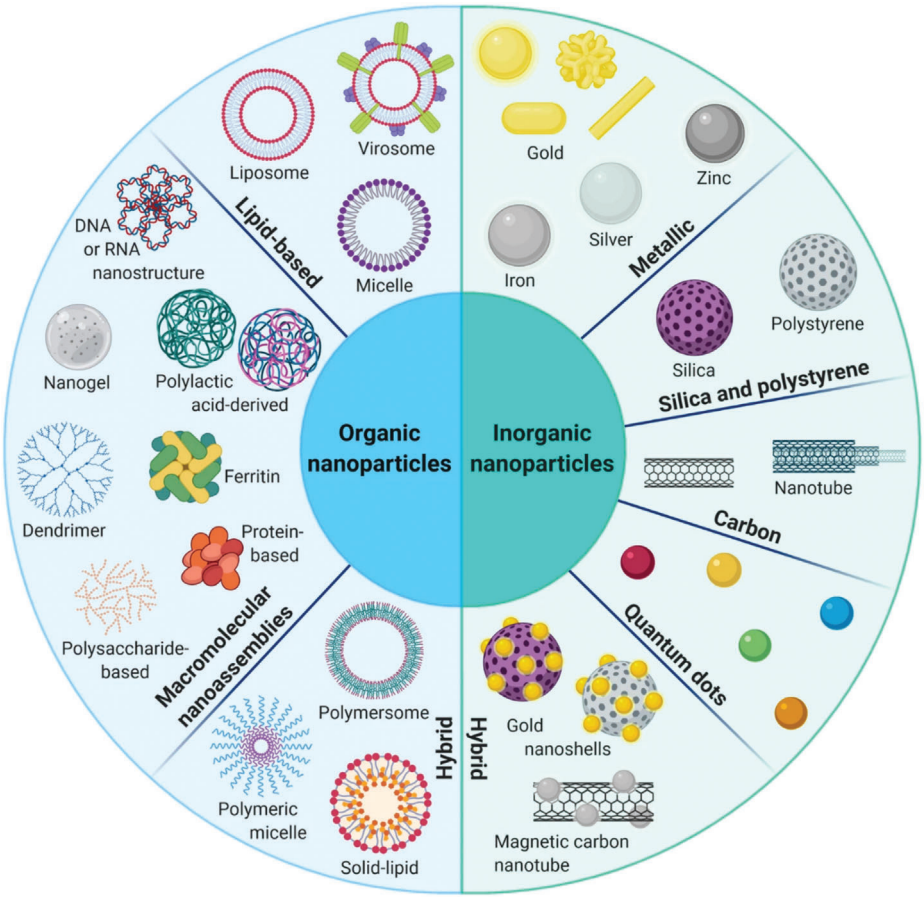

Figure 7. Schematic representation of most common nanoparticle-based drug delivery systems categorized based on chemical compositions. Reproduced under the term of CC-BY license.[57] Copyright 2021, The Authors, published by Springer Nature.

powder with sulfuric and nitric acids and precipitation using agents like potassium chlorate.[18] Techniques like chemical vapor deposition (CVD), HiPco, and CoMo CAT are employed, with CVD being cost-effective for large-scale production. It relies on a metallic catalyst, such as nickel or iron, and carbon gases like ethanol or acetylene for CNT growth.[18] Physical methods include laser ablation (LAM) and arc discharge (ADM). LAM heats graphite with a high-temperature laser, while ADM involves an ADM between pure graphite and a hydrated electrode in a helium-filled chamber with metal catalytic elements.[18] Other methods encompass rare approaches like flame synthesis, electrolysis, and helium ADM. Green synthesis, utilizing plant extracts, products, and oils, has been proposed as an eco-friendly alternative, reducing production costs and dependence on high-temperature methods. Plant materials like bamboo culms, rice straw, neem, and other plant products such as camphor have been shown potential as green catalysts for CNT growth.[65]

4.1. Types of CNTs

CNTs are categorized into three categories based on their number of tubular layers, that is, single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs), and multi-walled carbon nanotubes (MWCNTs) (**Figure 8** and **Table 3**).

4.1.1. SWCNTs

CNTs with a single layer of graphene, with a hexagonal structure, wrapped cylindrically and stabilized with van der Waals force, which makes SWCNTs more tunable for carrying therapeutic biomolecules such as proteins and genes.[18] The size of the wall ranges from 0.4 nm to several nm in diameter.[66] Cell penetration easiness, drug loading capacity, and circulation half-life are more than MWCNTs, making them suitable for nanocarrier and widely used in electrical, chemistry, sensor technology, and medical industries, predominantly cancer therapy, cell manufacturing, and bio-imaging.[18,67]

4.1.2. DWCNTs

DWCNTs have two cylindrical layers of graphene sheet; one lederhosen surrounded by the second layer. Electrical property is slightly changed in DWCNTs, whereas all other mechanical, optical, and chemical properties remain the same compared to

Table 2. Nanoparticle-based antifungal drug delivery systems.

Antifungal drugs	Delivery systems	Fungal species	Refs.
Amphotericin B	Solid lipid NPs, silica NPs, polymeric nanoparticles, magnetic NPs, nanoemulsionoil-in-water or water-in-oil, chitosan, hydrogel, chitosan-PLGA NPs, PLGA, gelatin NPs, chitosan-coated lipid NPs, Cu(II) complex, polyglucos, chitosan and porphyrin, bovine serum albumin (BSA), pectin polysaccharide	*Candida* spp.; *C. albicans*, *C. neoformans*, *C. parapsilosis*, *Aspergillus* spp.; *A. fumigatus*, *A. flavus*, *A. niger*, *Trichophyton* spp.; *T. rubrum*, *Fusarium* spp.; *F. solani*	[3,35,56,58]
Miconazole	Solid lipid NPs, nanoemulsion oil-in-water or water-in-oil, microemulsion, nanosponges, iron oxide–chitosan, chitosan	*Candida* spp.; *C. albicans*	[3,35]
Econazole	Solid lipid NPs, polymeric micelles, microemulsion, nanoemulsionoil-in-water or water-in-oil, nanosponges	*Candida* spp.; *C. albicans*	[3]
Ketoconazole	Solid lipid NPs	*Candida* spp.; *C. albicans*	[3]
Clotrimazole	Solid lipid NPs, polymeric micelles, microemulsion	*Candida* spp.; *C. albicans*	[3,58]
Itraconazole	Solid lipid NPs, silica NPs, polymeric nanoparticles	*Fusarium* spp.; *F. culmorum Trichophyton* spp.; *T. Rubrum*	[3,32,35]
Fluconazole	Solid lipid NPs, polymeric micelles, titanium oxide, copper NPs, silver-based NPs, chitosan	*Candida* spp.; *C. albicans, Fusarium* spp.; *F. semitectum, Rhizoctonia* spp.; *R. solani, Aspergillus* spp.; *A. graveolens, A. fumigatus, A. flavus, Saccharomyces* spp.; *S. cerevisiae*	[3,35,59]
Voriconazole	Solid lipid NPs, polymeric nanoparticles	*Candida* spp.; *C. albicans, C. auris*	[3]
Naftifine	Polymeric micelles		[35]
Caspofungin	Gold-based	*Candida* spp.; *C. albicans, C. glabrata, C. tropicalis*	[35,59]
Griseofulvin	Microemulsion		[58]
Micafugin	Silver-based NPs		[35]

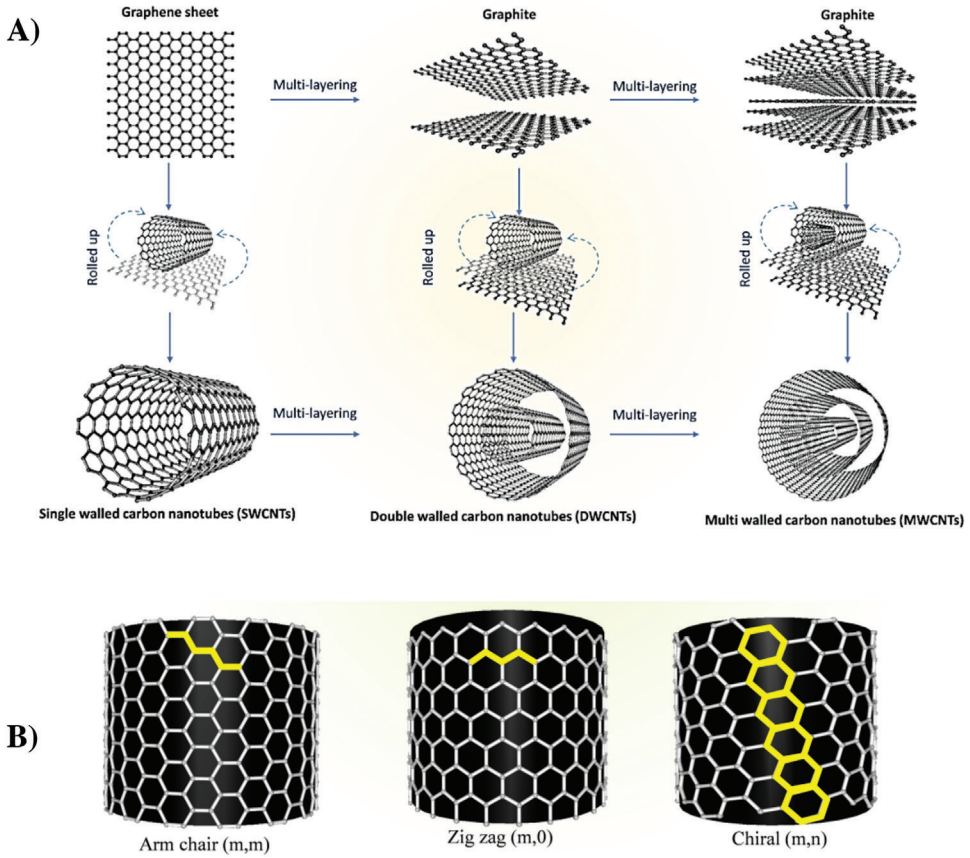

Figure 8. Illustrative image of types of CNTs. A) Categorized into three categories based on their number of tubular layers, that is, SWCNTs,DWCNTs, and MWCNTs. B) Categorized into three categories based on their symmetry, that is, armchair, zig-zag, and chiral form; (the authors designed the images using ChemDraw Pro 8.0 (PerkinElmer) and Microsoft PowerPoint).

Table 3. CNT types and their attributes.

Types of CNT	Diameter of innermost wall (in nm)	Thermal stability		Thermal conductivity		Mechanical strength		Methods of synthesis	Refs.
		In Ar	In air	By CVD	By arc-discharge	Tensile strength	Young's modulus		
SWCNTs	0.4 to several	≈1800 °C	750 °C	≈600 Wm^{-1} K^{-1}	>3500 Wm^{-1} K^{-1}	≈1.0 TPa (E)	≈1.8 TPa (E + T)	Arc-discharge, laser ablation, CVD	[66]
DWCNTs	0.33 to 0.42	≈2000 °C	800 °C	≈600 Wm^{-1} K^{-1}	-	13–46 GPa (E)	0.73–1.33 TPa (E)	Arc-discharge, Peapod method, CVD	[66]
MWCNTs	0.34	Varies	Varies	42–343 Wm^{-1} K^{-1}	>3000 Wm^{-1} K^{-1}	11–63 GPa (E)	0.27–0.95 TPa (E)	Arc-discharge, laser-ablation, Peapod method, CVD	[66]

SWCNTs.[68] Thermal stability of DWCNTs (stable in Ar up to ≈2000 °C, in air 800 °C and ≈600 Wm^{-1} K^{-1} thermal conductivity produced by CVD) is higher than SWCNTs (Stable in Arup to ≈1800 °C, in air 750 °C and ≈600 Wm^{-1} K^{-1} thermal conductivity produced by CVD), and Mechanical strength of DWCNTs (0.73–1.33 TPa (E + T) Young's modulus, and 13–46 GPa (E) Tensile strength) is higher than SWCNTs (≈1.8 TPa (E + T) Young's modulus, and ≈1.0 TPa (E) Tensile strength) due to presence of layers.[66] Reportedly, DWCNTs are also used as NCs with additional chemical pre-treatment such as oxidation, coating polymer then conjugate with modified desire biomolecules such as small interfering RNA (siRNA),[69] therapeutic drugs such as Doxorubicin,[70] etc.

4.1.3. MWCNTs

More than two layers of concentric tubular graphene are contained in MWCNTs, owing to the largest surface area for loading desired drugs compared to other CNTs. Electron delocalization occurs due to the configuration and structure of MWCNTs; sp^2 hybridization and π–π interaction among adjacent graphene layers result in the fate of low flexibility and structural alteration.[18] The stability of thermal varies concerning diameter and length, with very high thermal conductivity (>3000 Wm1 K1) and mechanical strength (0.27–0.95 TPa (E) Young's modulus, and11–63 GPa (E) Tensile strength).[66] Wall-nut (*Juglans regia*), neem (*Azadirachta indica*), garden grass (*Cynodondactylon*), and rose (Rosa) have been used to grow MWCNTs.

5. CNT Functionalization and CNT-HMs Synthesis

The surface functionalization of CNT (F-CNT) permits the conjugation of diverse organic and inorganic substances onto CNTs, forming CNT-HMs or nanocomposites.[17,22] Sol-gel methods,[17] hydrothermal methods,[17] and other chemical methods[22] [71]have been used to produce various CNT-HMs. CNT-HMs, including CNTs/polymer composites (e.g., polythiophenes, polyaniline, PANI, polypyrrole), CNTs/metal oxides (RuO_2, TiO_2, MgO, CeO_2), CNT/non-metal oxides (e.g., graphene oxide), and CNT/nanoparticles (e.g., platinum), have been extensively investigated for diverse applications, including supercapacitors, biosensors, solar cells, radar-absorbing materials, corrosion resistance, and small molecule carriers.[72] However, the solvent insolubility, poor dispersion characteristics, and natural tendency for agglomeration in CNTs constrain their utility in biomedical applications.[73] Mechanical (ultrasonication, high-shear) and chemical (functionalization, surface modification) methods address these constraints.[73] Functionalization can be categorized into two categories named exohedral and endohedral functionalization. Functionalization of the outer surface of side walls (exohedral) of CNTs done via covalent and non-covalent bonds can further be divided into two categories named covalent functionalization and non-covalent functionalization, whereas numerous functional groups or molecules bind on inner cavity (endohedral) of CNTs done via encapsulation methods[16] (**Figure 9**).

5.1. Exohedral Covalent Functionalization

The covalent bond that irreparably and irreversibly attaches active chemical groups such as carboxylic groups, fluorine, auxiliary dichloro-carbon, and p-aminobenzoic acid groups to carbon atoms located on the wall surface or end tip of the CNTs, which results in the transformation of sp^2 hybridization into sp^3 hybridization and enhancement of the dispersibility and bioavailability of CNTs.[16,74] This process has been classified into two classes, that is, direct and indirect covalent functionalization.[74] SWCNTs were reported to be easier to functionalize than other forms of CNTs, such as DWCNTs and MWCNTs because multiple walls shielded the other walls.[74] The most common method of covalent functionalization has been achieved by oxidation of CNTs employing various oxidizing chemicals such as nitric acids (HNO_3) and sulfuric acids, which results in the carboxylic group formation at the end and the surfaces and sidewall of the CNTs.[74] Cycloaddition reaction (nucleophilic) also takes place to the sidewall of CNTs followed by three methods; photoinduced (azide production), Bingal (carbene production), and 1,3-dipolarcycloadditions.[16,74]

5.2. Exohedral Non-Covalent Functionalization

The hydrophobic region of foreign molecules interacted with the sidewalls of CNTs through various non-covalent bonds such as Van der Waal's force, hydrophobic, and π–π interactions.[16] This functionalization does not substantially damage or disrupt the arrangements of CNTs and preserves their electronic

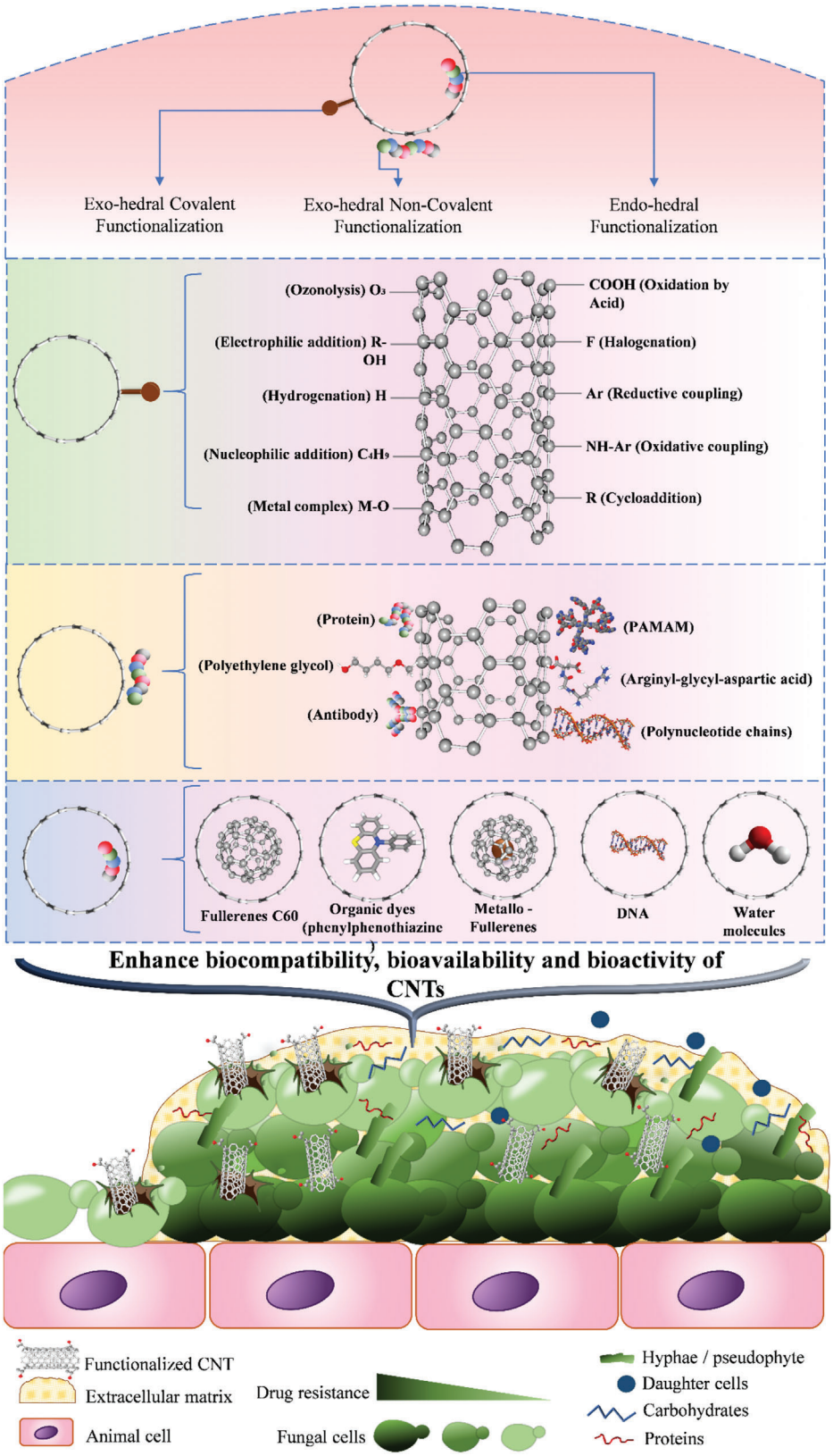

Figure 9. Schematic illustrative image of types of F-CNTs, their effects in antifungal activity, and biocompatibility; (the authors designed the pictures using ChemDraw Pro 8.0 (PerkinElmer) and Microsoft PowerPoint).

properties.[16,74] Dispersion of surfactants (both ionic surfactants and non-ionic surfactants, such as cetyltrimethyl ammonium bromide, sodium dodecyl sulfate (SDS), sodium dodecyl benzenesulfonate, Brij, Triton X, Tween), deposition of metals (e.g., Cu, Au, Ag, Pd, Pt, Ni and Ti), wrapped with polymers (such as polyvinyl pyrrolidone and polystyrene sulfonate), absorption of polymers (such as proteins and biomolecules), and encapsulation of polymers (such as n-butyl acrylate, methyl methacrylate) has been involved in exohedral non-covalent functionalization.[16]

5.3. Endohedral Functionalization

Numerous active molecules can be encapsulated into highly new and high-bond energy-containing inner cavities of CNTs.[16] Encapsulation of metal (such as Fe, Co, Ni, Ti, Cu), encapsulation of fullerene (C_{60}, C_{70}, metallofullerenes), and encapsulation of various miscellaneous molecules (such as halogen element) into the cavity of CNTs have been involved.[16]

5.3.1. Applications of CNTs and CNT-HMs

CNTs are utilized extensively in many applications, such as energy conversion, storage, water treatment, and biomedical applications. Primary biomedical application of CNTs includes drug delivery,[19] gene delivery,[19] bio-imaging,[19] biosensors,[19] tissue engineering,[19] tissue regeneration,[19] and cancer treatment. CNTs are employed as bioelectronics, tissue constructors, bio-imaging tools, biosensors, and nanocarriers.

5.3.2. CNT and CNT-HMs as a Tissue Constructor

CNT-based scaffolds and bio-scaffolds (CNTs combined with polymethyl methacrylate resin matrix) have excellent biocompatibility, electrical conductivity, mechanical strength (up to 1 TPa tensile strength up to 100 GPa, Young's modulus) and biodegradability properties can help in tissue engineering for stem cell proliferation and differentiation applications.[75] MWCNT-containing electrospun nanofiber scaffolds in rats showed outstanding peripheral nerve cell regeneration capabilities.[76] CNT-based scaffolds can be formulated by combining CNT with natural polymers, synthetic polymers, and calcium phosphate and extensively reported and explored in numerous tissue engineering applications such as tumor (self-assembling peptide-CNT),[77] retinal (CNT/poly D,L,-lactic-*co*-glycolic acid scaffold),[75] bone (CNT/carboxymethyl/chitosan hydrogel),[78] myocardial, neural (CNT/chitosan/polyethylene glycol (PEG)),[79] cartilage (polycaprolactone/chitosan/CNT) tissue engineering.

5.3.3. CNT and CNT-HMs as Bio-Imaging and Biosensor Tools

The vast surface area of CNT-based biosensor probes enables the immobilization of several functional molecules, including sensors for biosensing.[73] CNT-based biosensors were developed by coupling biomolecules to CNT and chemical functionalization of CNT. The coupling of biomolecules includes DNA or antibodies, aptamers, enzymes, proteins, and peptides, whereas chemical functionalization, that is, amine with folic acid, is used for visualization of the cancer cells.[73]

5.3.4. CNT and CNT-HMs as a Nanocarrier

CNTs serve as exceptional nanocarriers due to their high aspect ratio (higher drug loading capacity), ease of functionalization (ensure versatile payloads, biocompatibility, bioavailability, and reduced toxicity of drug), nanoneedle shape (competence to penetrate across plasma membranes), drug encapsulation in core space (prolonged circulation half-life and protection of the drug from cytosolic enzyme degradation), controlled drug release, excellent mechanical strength (biostability) making them promising drug and gene delivery systems.[18,23] Also, CNT and CNT-HMs-based DDSs attribute enhanced pharmacokinetics, pharmacodynamics, pharmaceuticals, and pharmacotherapy, offering benefits like improved bioavailability and patient adherence while reducing toxicities.[80,81] These attributes render them the most prominent delivery vectors compared to conventional DDSs.[18,23] For example, Mody et al. conducted a comparative analysis involving MWCNTs, LIP, nanoparticles (NPs), and dendrimers. Their investigation revealed that the MWCNT hybrid exhibited a significantly enhanced entrapment efficiency of $74.70 \pm 4.92\%$, surpassing that of the other scrutinized nanocarriers, namely DTX-LIP (49.2 ± 1.5), DTX-NP (62.34 ± 1.51), and DTX-DEN (28.26 ± 1.74). Furthermore, the toxicology assessment conducted on human cervical cancer SiHa cells demonstrated that the CNT hybrid displayed the lowest IC50 value of 1235.09 ± 41.93 nM, in contrast to the other variants DTX-DEN (IC50: 1571.22 ± 151.27 nM), DTX-LIP (IC50: 1653.98 ± 72.89 nM), and DTX-NP (IC50: 1922.75 ± 75.15 nM).[82] In a study by Wang et al., CNT hybrid conjugates with folic acid and protohemin were compared to liposomal-based DDS. The CNT hybrid DDS exhibited significantly higher growth inhibition rates ($95.4 \pm 5.9\%$) than liposomal DDS ($42.3 \pm 2.9\%$) in vitro, showcasing enhanced therapeutic efficacy.[83] Moreover, many researchers have studied (in vivo and in vitro studies) and proved that the CNTs could efficiently deliver a range of medicinal and pharmaceutical drugs, such as antiviral drugs, anti-bacterial drugs, anti-fungal drugs, anti-leishmaniasis drugs, anti-cancer drugs, neurological drugs, antioxidants, anti-inflammatory drugs, anti-hypertensive drugs, wound-healing drugs, immuno-suppressant drugs, immune-stimulatory drug, immune-adjuvant drugs, anti-hemorrhagic drug, anti-protozoan drugs, antigenic proteins, and so on. The most popular medications delivered concerning types of CNTs; listed in **Figure 10**.

6. CNTs: An Efficient and Promising System for Antifungal Drug Carrier and Delivery

Only 1% of drugs delivered via direct conventional drug delivery reached the target site of the cell, while the remaining 99% experienced deleterious repercussions. This drug delivery percentage can be increased using a CNT-based DDS. F-CNTs can bind with the drug (exohedral or endohedral), deliver it to the target

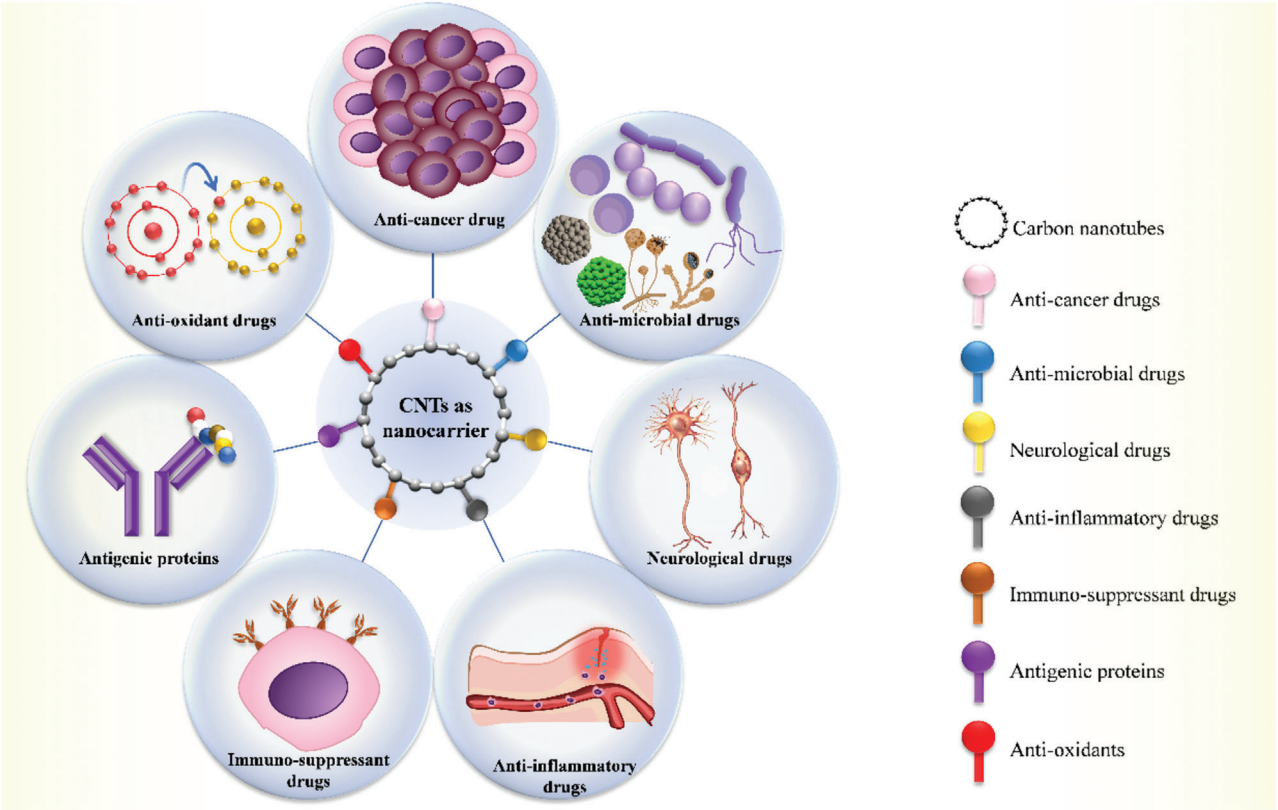

Figure 10. Schematic illustration of CNTs as nanocarriers successfully delivered drugs and other therapeutics agents; (the authors designed the images by using ChemDraw Pro 8.0 (PerkinElmer) and Microsoft PowerPoint).

site, and penetrate the cellular barrier. Many types of therapeutic molecules and drugs that CNT-HMs-based delivery systems have produced are listed in **Table 4**.

6.1. Antimicrobial and Antifungal Activity of CNTs and CNT-HMs

These antimicrobial and antibiofilm activities of CNT and CNT-HMs can be influenced by various factors such as the geometry of CNTs (such as length of tubes,[22] number of side walls), purity of CNTs (such as pristine CNTs, F-CNTs, CNT-HMs), types or strain of microorganism (such as gram-positive and negative bacteria,[22] fungal species), dosage,[22] and types of hybrid material present on CNT walls.[22] Shorter-CNTs, CNT-HMs, and MWCNTs have more antimicrobial activity than longer-CNTs, pristine-CNTs, and SWCNTs, respectively, due to interactions with cell membranes and subsequent cell disruption, reduce the cell surface hydrophobicity and suppress the transcription process of the oxidative stress-resistance genes.[22] Gram-positive bacteria have been less susceptible to CNT-HMs than gram-negative bacteria due to a thicker peptidoglycan coating.[22]

6.2. Antifungal Drug Loading

The active forms of the antifungal drug can be loaded into F-CNTs by numerous types of linkage, such as covalent (chemical conjugations), non-covalent link (physical adsorption), or metallic NPs.[87] Antifungal drugs such as AMB have been conjugated successfully with functionalized MWCNTs (F-MWCNTs) by Pruthi et al. in 2012 for the targeted delivery to macrophage "J774" cell line. AMB loading efficiency of various f-MWCNTs forms such as purified MWCNTs (AMB/MWCNT), Carboxylated MWCNTs (AMB/carboxyl-MWCNTs), aminated MWCNTs (AMB/amine-MWCNTs), mannosylated MWCNTs (AMBitubes) were estimated by dialysis membrane methods. AMBitubes have exhibited the highest (75.46 ± 1.40%) drug loading efficiency, followed by AMB/carboxyl-MWCNTs (66.80 ± 2.18%), AMB/amine-MWCNTs (62.06 ± 1.59%), and AMB/MWCNT (54.00 ± 2.43%). The AMB (by Wu et al., Vikelouda et al.,) and other antifungal or therapeutic molecules such as NYS (by Utekar et al., Helal et al.), FLC (by Helal et al.), lysine (by Zare-Zardini et al.), arginine (by Zare-Zardini et al.) have been successfully loaded into CNTs and achieved significant antifungal activity (in vitro) for various fungal species, which could result in several benefits, such as enhanced efficacy (due to their clustering effect with higher CNT cellular internalization capability), increased molecular bioavailability, avoiding agglomeration, and greater specificity to target cells over host cells, resulting in an improved therapeutic index.[87] PEG chains can also be loaded to maximize the dispersibility of CNTs.[87] Antifungal drugs AMB loaded into CNT and their loading efficiency has been investigated by Benincasa et al. (**Table 5** and **Figure 11**).

Table 4. Different types of drugs delivered by CNTs.

Types of CNT	Drug type	Drugs	Refs.
SWCNTs	Antiviral drugs	Koi herpes virus DNA vaccine, CHI415, and CHI360	[18,74]
	Anti-bacterial drugs	Curcumin, silver	[18,74]
	Anti-fungal drugs	AMB,	[84]
	Anti-leishmaniasis drugs	Cisplatin	[74]
	Anti-cancer drugs	DTX, DOX, DAU, THP, MTX, CDDP, PTX, TAM, thalidomide, HMM, Ce6, HMME, hyaluronic acid, camptothecin, curcumin	[65,74,84,85]
	Neurological drugs	Acetylcholine, levodopa, dopamine	[18]
	Antioxidants	TPGS, quercetin rutin, curcumin	[74,84]
	Anti-inflammatory drugs	DEX phosphate	[74,84]
	Wound-healing drugs	FBS, penicillin/streptomycin, chitosan	[74]
	Immuno-suppressant drugs	Cyclosporin A (CsA)	[74]
	Anti-hemorrhagic drugs	Carbazochrome	[86]
	Other drugs	nEGFP,[85] carnosine dipeptide	[85]
DWCNTs	Anti-protozoan drugs	Chloroquine	[84]
MWCNTs	Antiviral drugs	CHI415 and CHI360	[18]
	Anti-bacterial drugs	Dapsone,[84] pazufloxacin mesilat,[84] gentamicin-ionic, and non-ionic surfactant	[18,84]
	Anti-fungal drugs	AMB, lysine, arginine	[73,84]
	Anti-cancer drugs	DTX, DOX, polyethyleneimine, ABT-737, HCPT, CPT, EPI, irinotecan, etoposide, oxaliplatin, MTX, PTX, catechin, HMM, 5-aminolevulinic acid, gemcitabine, cisplatin, pemetrexed, quercetin	[18,65,74,84,85]
	Anti-inflammatory drugs	DEX phosphate, diclofenac sodium, ketoprofen, indomethacin	[84]
	Anti-hypertensive drugs	Diltiazem hydrochloride, metoprolol tartrate, candesartan cilexetil, diltiazem hydrochloride, carvedilol	[84]
	Antioxidant drugs	TPGS, gallic acid	[84]
	Antigenic proteins	Ovalbumin	[74,85]
	Wound-healing drugs	FBS, penicillin/streptomycin	[74]
	Immune-stimulatory drug	Lentinan	[73]
	Immune-adjuvant drugs	Anti-CD40 Ig and cytosine phosphate guanine oligodeoxynucleotide (CpG-ODN)	[73]
	Other drug	Zolpiden	[85]

DNA, Deoxyribose Nucleic Acid; CHI415, 4-amino-1-(3,5-dimethylphenylsulfonyl)−1,3-dihydro-2Hbenzimidazol-2-one; CHI360, 4-amino-1-(3,5-dimethylbenzyl)−1,3-dihydro-2H-benzimidazol-2-one; AMB, Amphotericin B; DTX, Docetaxel; DOX, Doxorubicin; DAU, Daunorubicin; THP, Pirarubicin; MTX, Mitoxantrone; CDDP, Cis-diammine-dichloroplatinum; PTX, Paclitaxel; TAM, Tamoxifen; HMM, Hexamethylmelamine; Ce6, Chlorine 6; HMME, Hematoporphyrin monomethyl ether; TPGS, Tocopheryl PEG succinate; DEX, Dexamethasone; FBS, Fetal bovine serum; non-functional enhanced green fluorescence protein, nEGFP, HCPT, 10-Hydroxycamptothecin; CPT, Camptothecin; EPI, Epirubicin; TPGS, Tocopheryl PEG succinate.

6.3. Antifungal Drug Release

The mechanism of drug release from CNTs or CNTs-based NCs has been a crucial determinant of the therapeutic efficacy and adverse effects.[91] The drug release mechanism has been commonly determined by drug solubility and matrix degradation, molecular diffusion probabilities, drug permeation rate through the matrix, and surface-linked desorption or immobilized drug[92] (**Figure 12**A).

CNT Consequently, the diffusion, biodegradation, solubility of matrix materials, and couplings of the drug to CNTs by the van der Waals influence the drug release rate.[92] Studies revealed that drug release is accomplished in diffusion and matrix degradation. Nevertheless, the drug release rate can be regulated by the distribution process.[92] Additionally, several mathematical operations include zero, first and second-order kinetics, Higuchi, Hixson–Crowell, Ritger-Peppas/Korsmeyer–Peppas (power-law model), and Weibull can be applied to illustrate the release mechanism.[93,94] The zero-order model has a constant drug release rate across time, whereas in the first-order model, the release of the drug is directly proportional to the drug concentration.[94] The Higuchi model explains the release rate as a function of the square root of time, and its generalized model is termed the Korsmeyer-Peppas model.[94] The equations for all the models described above are:

$$\text{Zero} - \text{Ordermodel};\ \mathrm{M_t} = \mathrm{M_\infty} + \mathrm{kt} \tag{1}$$

$$\text{First} - \text{Order model};\ \ln\left(M_t/M_\infty\right) = kt \tag{2}$$

$$\text{Higuchi model};\ M_t/M_\infty = k\sqrt{t} \tag{3}$$

$$\text{Korsmeyer} - \text{Peppas model};\ \ln\left(M_t/M_\infty\right) = \ln k + n\ln t \tag{4}$$

Table 5. Antifungal drugs loaded into CNTs or CNTs-based NCs with their antifungal activity.

Types of CNT	Loaded drug	Surface modification; % [w/v]	Fungal species	Dose [μg mL^{-1}]	Method for determining antifungal activity	Incubation period	Antifungal activity (MIC_{50}/MFC_{50} value)	Efficiency	Cytotoxic effect and cell line (in vitro)	Refs.
SWCNT	Amphotericin B (AMB)	Polyethylene glycol (PEG); 10%	*Candida albicans*	80	MIC	3 h	>80 (>8 μg mL^{-1})	99.9%	Significantly not toxic on Jurkat mammalian cell line (JMCL)	[87]
SWCNT	AMB	PEG; 10%	*Candida neoformans*	20	MIC	3 h	2.5 to 10 (0.25 to 1 μg mL^{-1})	99.9%	Significantly not toxic on JMCL	[87]
SWCNT	AMB	—COOH	*Candida albicans*	-	-	48 h	13.8 μg mL^{-1}	-	Significantly not toxic on JMCL	[88]
SWCNT	AMB	—COOH	*Candida neoformans*	-	-	48 h	0.8 μg mL^{-1}	-	Significantly not toxic on JMCL	[88]
SWCNT	AMB	—COOH	*Candida parapsilosis*	-	-	48 h	1.6 μg mL^{-1}	-	Significantly not toxic on JMCL	[88]
SWCNT	F-SWCNT	—COOH; 2.83%	*Fusarium graminearum*	500	MFC	3 h	Not reported	>95.2%	Not reported	[96]
SWCNT	F-SWCNT	—COOH; 2.83%	*Fusarium poae*	500	MFC	3 h	Not reported	>90.8%	Not reported	[96]
SWCNT	F-SWCNT	-	*Candida albicans*	100	CFU	24 h	Not reported	95%	-	[97]
SWCNT	F-SWCNT	NH3+	*Candida albicans*	-	-	48 h	>80 (>8 μg mL^{-1})	-	Significantly not toxic on JMCL	[98]
SWCNT	F-SWCNT	NH3+	*Candida neoformans*	-	-	48 h	>80 (>8 μg mL^{-1})	-	Significantly not toxic on JMCL	[98]
SWCNT	fSWCNT	NH3+	*Candida parapsilosis*	-	-	48 h	>80 (>8 μg mL^{-1})	-	Significantly not toxic on JMCL	[98]
DWCNT	F-SWCNT	-	*Candida albicans*	100	CFU	24 h	Not reported	40%		[99]
MWCNT	AMB	PEG; 10%	*Candida albicans*	80	MIC	3 h	10 (2.5 μg mL^{-1})	99.9%	Significantly not toxic on JMCL	[87]
MWCNT	AMB	PEG; 10%	*Candida neoformans*	20	MIC	3 h	0.3 to 2.5 (0.075 to 0.6 μg mL^{-1})	99.9%	Significantly not toxic on JMCL	[87]
MWCNT	AMB	—COOH	*Candida albicans*	-	-	48 h	6.4 μg mL^{-1}	-	Significantly not toxic on JMCL	[18,88]
MWCNT	AMB	—COOH	*Candida neoformans*	-	-	48 h	0.8 μg mL^{-1}	-	Significantly not toxic on JMCL	[88]
MWCNT	AMB	—COOH	*Candida parapsilosis*	-	-	48 h	1.6 μg mL^{-1}	-	Significantly not toxic on JMCL	[88]
MWCNT	F-MWCNT	—COOH; 3.86%	*Fusarium graminearum*	500	MFC	3 h	Not reported	85.5%	Not reported	[96]
MWCNT	F-MWCNT	—COOH; 3.86%	*Fusarium poae*	500	MFC	3 h	Not reported	84.4%	Not reported	[96]
MWCNT	F-MWCNT	Argon	*Candida albicans*	100	CFU	24 h	Not reported	60%	Not reported	[99]
MWCNT	fMWCNT	-OH; 3.7%	*F. graminearum*	62.5	CFU	48 h	-	>75%	-	[100]
MWCNT	F-MWCNT	-NH3; 0.45%	*F. graminearum*	500	CFU	48 h	-	>75%	-	[100]
MWCNT	F-MWCNT	—COOH;	*F. graminearum*	250	CFU	48 h	-	>75%	-	[100]
MWCNT	MWCNT	-	*B. cinerea*	5000	-	-	-	-	-	[101]
MWCNT	Lysine	—COOH	*Aspergillus niger*	5 μg	MIC	24 h	29 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Aspergillus fumigatus*	5 μg	MIC	24 h	10 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Candidate albicans*	5 μg	MIC	24 h	15 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Penicillium chrysogenum*	5 μg	MIC	24 h	18 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Saccharomyces cerevisiae*	5 μg	MIC	24 h	20 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Fusarium culmorum*	5 μg	MIC	24 h	15 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Microsporumcanis*	5 μg	MIC	24 h	12 μg mL^{-1}	-	-	[102]

(*Continued*)

Table 5. (Continued).

Types of CNT	Loaded drug	Surface modification; % [w/v]	Fungal species	Dose [μg mL^{-1}]	Method for determining antifungal activity	Incubation period	Antifungal activity (MIC_{50}/MFC_{50} value)	Efficiency	Cytotoxic effect and cell line (in vitro)	Refs.
MWCNT	Lysine	—COOH	*T. mentagrophytes*	5 μg	MIC	24 h	14 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Trichophyton rubrum*	5 μg	MIC	24 h	13 μg mL^{-1}	-	-	[102]
MWCNT	Lysine	—COOH	*Penicillium lilacinum*	5 μg	MIC	24 h	10 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Aspergillus niger*	5 μg	MIC	24 h	22 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Aspergillus fumigatus*	5 μg	MIC	24 h	10 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Candidate albicans*	5 μg	MIC	24 h	16 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Penicillium chrysogenum*	5 μg	MIC	24 h	15 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Saccharomyces cerevisiae*	5 μg	MIC	24 h	19 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Fusarium culmorum*	5 μg	MIC	24 h	11 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Microsporumcanis*	5 μg	MIC	24 h	11 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*T. mentagrophytes*	5 μg	MIC	24 h	13 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Trichophyton rubrum*	5 μg	MIC	24 h	13 μg mL^{-1}	-	-	[102]
MWCNT	Arginine	—COOH	*Penicillium lilacinum*	5 μg	MIC	24 h	10 μg mL^{-1}	-	-	[102]
MWCNT	NYS	—COOH/amide	*Candida albicans*	-	MIC/MFC	24 h	6/16	-	-	[98]
MWCNT	NYS	—COOH/amide	*Candida parapsilosis*	-	MIC/MFC	24 h	4/14	-	-	[98]
MWCNT	NYS	—COOH/amide	*Candida neoformans*	-	MIC/MFC	24 h	2/11	-	-	[98]
MWCNT	NYS	-COOH	-	-	-	-	-	-	-	[90]
MWCNT	FLZ	-COOH	-	-	-	-	-	-	-	[90]
CNT	TiO_2	-	*Candida albicans*	-	OD	5 h	-	>75%	Not reported	[59]
CNTs	AMB deoxycholate	PEG	*Candida albicans and Candida parapsilosis*	≥1	MIC	24 h	1 mg L^{-1}	83%	Not reported	[103]

where M_t represents the absolute cumulative concentration of the drug released at time t, M_∞ represents the total cumulative concentration released after infinite time, k represents the release kinetic constant, and n represents the diffusion exponent parameter.[94]

Drug release rates have also been influenced by the nature of the drug (hydrophilicity, solubility), the strength of linkage (amide in AMB), and physiological conditions (pH, time) of the medium.[94] Plain AMB solution, AMB-loaded pure MWCNTs (AMB-NT), and AMB-loaded mannosylated MWCNTs (AmBitubes) have been set for in vitro drug release studies at three different physiological conditions (such as pH 4, 7, and 10) by Pruthi et al.[95] The higher AMB drug release at pH 4 was monitored from AMB-NT and AmBitubes than pH 7.4 due to the amphoteric nature of AMB; at high pH, the hydrophilicity of AMB increased. Similarly, in vitro drug release was investigated by Yazdani et al., at two different (pH 5.5 and 7.4) mediumsfor AMB loaded on double-functionalized SWCNTs (DF-SWCNTs), and their cumulative release profile displayed in Figure 12A,B. Helal et al., investigated NYS and FLC drug release from F-CNT by Dialysis bag approach.[90] ≈97% (in 12 h) and 81% (in 12 h) cumulative drug release percentages were recorded for NYS and FLC from F-CNTs (Figure 12C,D).

6.4. In Vitro and In Vivo Studies on Antifungal Agents Loaded CNT CNT-Based Drug Delivery

In 2005, Wu et al. synthesized a CNT hybrid incorporating AMB and fluorescein. Subsequently, the hybrid's antifungal potential was examined against three pathogenic fungal species: *Candida albicans*, *Candida parapsilosis*, and *Cryptococcus neoformans*. The study concluded that judicious conjugation strategies could augment antifungal effectiveness, a deduction supported by thorough in vitro and in vivo evaluations.[88] Vossoughi et al., introduced the first amide-functionalized CNT-AMB hybrid using a diimide-activated amidation process for drug delivery application.[104] Benincasa et al. developed various AMB formulations, including sodium deoxycholate (AMB-SD), liposomal AMB, and AMB-loaded SWCNT hybrid (AMB-CNT). The in vitro study of AMB-CNT hybrids demonstrated MIC values comparable or superior to those of both AMB and AMB-SD. Resistant *Candida* strains were susceptible to AMB-CNT hybrid. Mechanistic insights indicated a nonlytic mode of action, with enhanced permeabilization observed after prolonged incubation. Significantly, in vivo investigation demonstrated that AMB-CNT hybrid displayed negligible cytotoxicity to Jurkat cells at concentrations relevant to antifungal activity[87] (**Figure 13**). Pruthi et al. synthesized AMB-mannosylated CNT hybrid (AmBitubes)

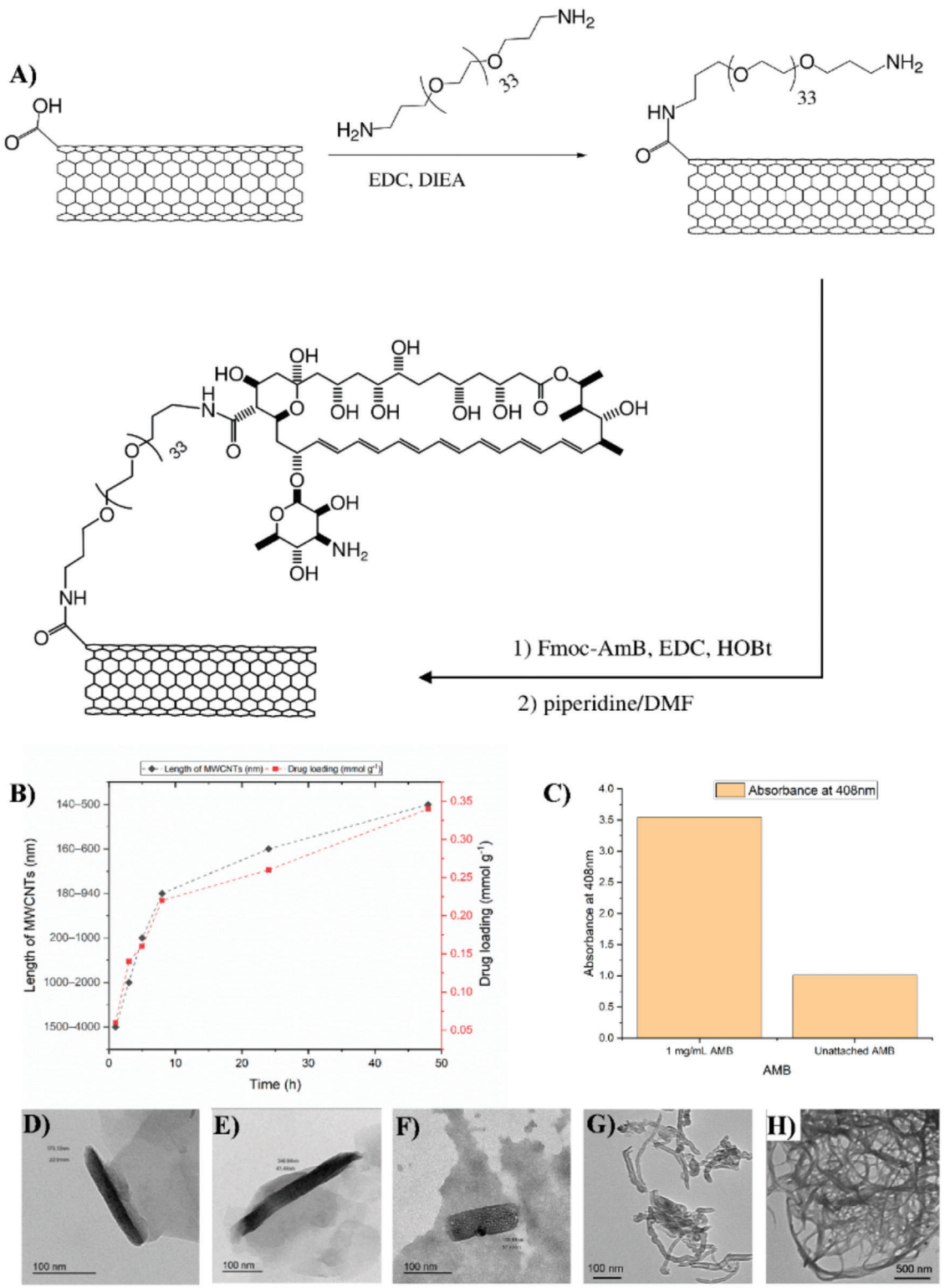

Figure 11. A) Illustrative image of steps involved in loading of AMB drug into F-CNTs. Reproduced with permission.[87] Copyright 2011, American Chemical Society. B) Loading of AMB drug concerning the length distribution of MWCNTs. Reproduced with permission.[88] Copyright 2005, WILEY-VCH GmbH. C) AMB drug loading efficiency determination by the UV–visible spectrophotometer, absorbance recorded at 408 nm of AMB solution (1 mg mL^{-1}), and unattached AMB from AMB loaded CNTs solution (the authors designed the figure by using OriginPro 2022), Reproduced with permission.[89] Copyright 2011, Oxford University Press. Representative TEM images: D) pristine MWCNTs, E) NYS loaded f-MWCNT, F) FLC loaded f-MWCNT. Reproduced with permission.[90] Copyright 2022, Springer Nature. Representative TEM images of G) AMB-loaded F-CNT-1 and H) F-CNT-2. Reproduced with permission.[88] Copyright 2005, WILEY-VCH GmbH.

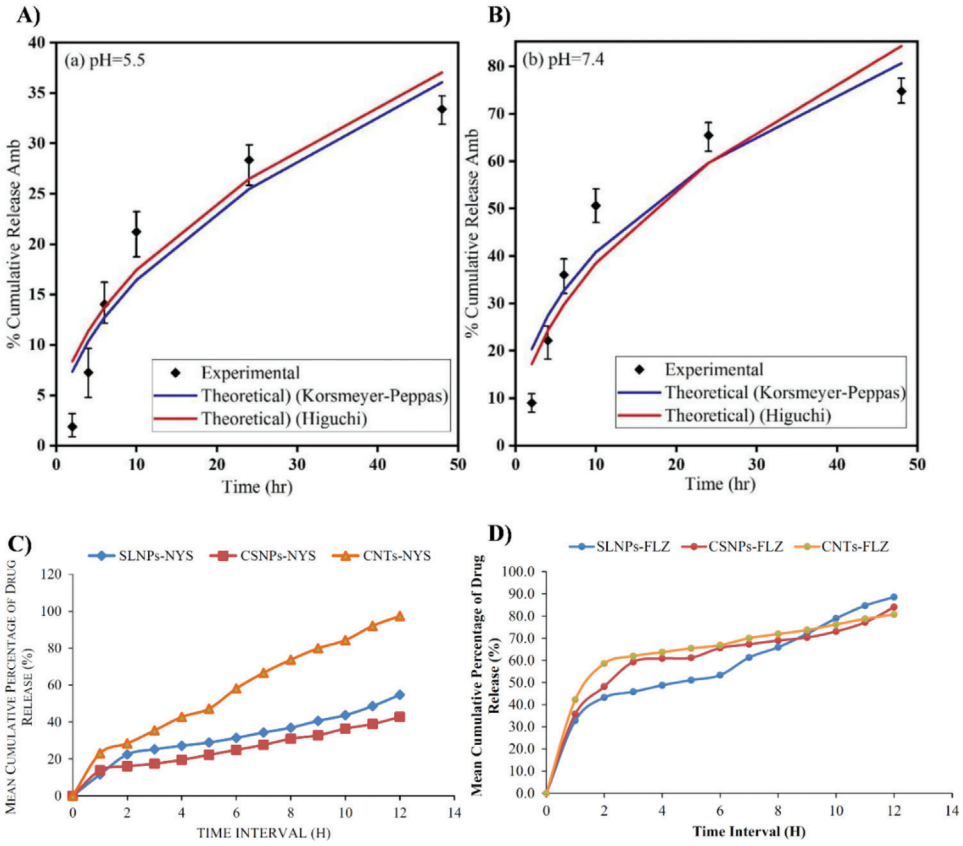

Figure 12. Cumulative release of AMB from AMB/DF-SWCNT formulation in medium with A) pH = 5.5 and B) pH = 7.4. Korsmeyer-Peppas kinetic and Higuchi models were applied for the study; Reproduced with permission under the term of CC-BY license https://creativecommons.org/licenses/by-nc-nd/4.0/.94.[94] Copyright 2022, The Authors, published by Springer Nature. Mean cumulative percentage release of drugs; C) NYS (in orange colored line with triangle symbol) and D) FLC (in yellow colored line with circle symbol) from F-CNTs. Reproduced with permission under the term of CC-BY license.[90] Copyright 2022, The Authors, published by Springer Nature.

showed 500 nm size, tubular structure, and high entrapment (75.46 ± 1.40%). They were investigated in vitro and in vivo for controlled AMB release (pH 4, 7.4, 10) with enhanced uptake and targeted distribution in macrophage-rich organs.[95] Zare-Zardini et al. reported the enhancement of MWCNTs' antifungal efficacy against *Aspergillus niger, Penicillium chrysogenum, Aspergillus fumigatus, Microsporum canis, Candidate albicans, Saccharomyces cerevisiae, Trichophyton mentagrophytes, Fusarium culmorum, Penicillium lilacinum,* and *Trichophyton rubrum* through covalent functionalization with lysine and arginine utilizing microwave radiation.[102] Yazdani et al. dual-functionalized the CNT hybrid with DSPE-PEG carboxylic acid and ethylenediamine, yielding DFCNTs as AMB and EGFP plasmid carriers. The in vitro investigation of AMB release was ≈33% and 75% at pH 5.5 and 7.4, respectively, in 48 h. In vivo investigation of functionalized CNT displayed reduced toxicity (CCK8).[94] In 2022, Helal et al. conducted in vitro comparisons of NYS-loaded CNT hybrid material with conventional DDSs, including solid lipid nanoparticles (SLNPs) and chitosan nanoparticles (CSNPs). The study found higher release percentages in NYS-loaded CNT hybrid material (97%) compared to other systems: SLNPs (55%) and CSNPs (43%).[90]

Pruthi et al. employed albino rats as animal models to study AMB-loaded CNT targeting macrophages.[95] Similarly, Prajapati et al. utilized a hamster model to demonstrate the oral administration potential of this novel AMB formulation, achieving a remarkable 99% inhibition of parasite growth with a 5-day course at 15 mg k^{-1} g body weight.[105] Shakoor et al. systematically investigated MWCNT pre-exposure effects on fungal infection toxicity in animal models such as nematodes and the underlying mechanisms.[106]

7. Spotlight on Toxicity Issues of CNTs

CNTs have toxicological and pathological effects such as cellular toxicity, inflammatory reaction, fibroblastic response, genotoxic effects, tumorigenesis, or immunotoxicity.[107] Nonfunctionalized (pristine) CNTs (PCNTs) act as foreign bodies in cells, triggering immune responses and oxidative processes, leading to inflammation and cytotoxicity. F-CNTs exhibit lower inflammation levels.[108] PCNTs induce oxidative stress, generating free radicals that damage DNA, proteins, and lipids, leading to inflammation.[108] CNTs can accumulate in organs, causing oxidative stress and toxicity. Functionalization makes CNTs more biocompatible and soluble, reducing toxicity.[108] Investigating CNTs for drug delivery in immunocompromised patients is vital for developing safe delivery methods.[108] Takanashi et al. implanted MWCNTs in rasH2 mice for carcinogenicity assessment,

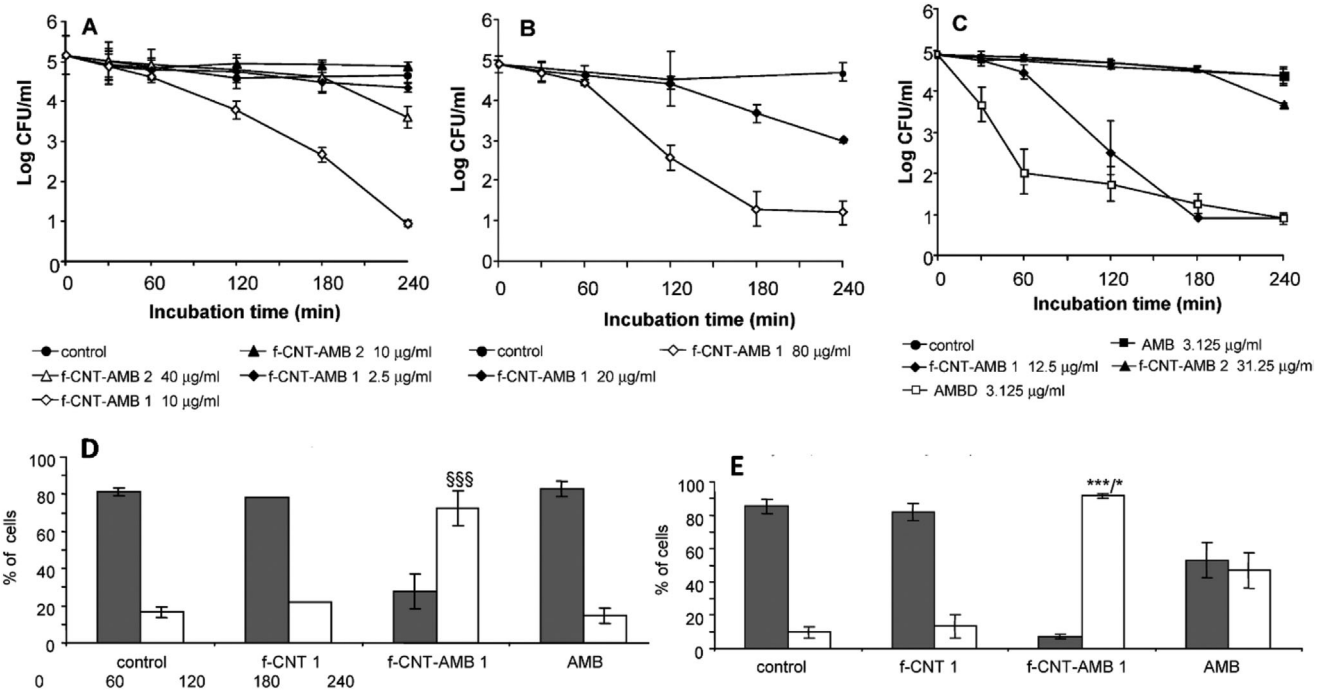

Figure 13. A) Attenuation kinetics of AMB loaded F-CNT 1 against *C. neoformans* L1. B) Attenuation kinetics of functionalized CNT-loaded antifungal drugs (AMB) against *C. albicans* L21. C) Attenuation kinetics of AMB loaded F-CNT 2 against *C. neoformans* L1. D) % of cells (*C. neoformans* L1) Undamaged or depolarized after 16h incubation with F-CNT and AMB loaded F-CNT . E) % of cells (*C. albicans* L21) Undamaged or depolarized after 16h incubation with F-CNT and AMB loaded F-CNT. Reproduced with permission.[87] Copyright 2011, American Chemical Society.

using carbon black from tattoo ink as a reference. MWCNTs showed lower carcinogenicity, with no neoplasms observed.[109] Suzui et al. assessed tumorigenesis by intratracheally administering MWCNTs to F344/Crj rats. In the control group, no tumor formation occurred, while in the MWCNT group, 6/38 rats developed malignant mesothelioma, and 14/38 displayed lung tumors (bronchiolo-alveolar adenomas and carcinomas).[110] In an in vitro setting, MWCNTs triggered the NF-κB signaling pathway, leading to an increased secretion of pro-inflammatory cytokines and chemokines, including TNF-R, IL-1β, IL-6, IL-10, and MCP1

Mohanta et al. investigated that CNTs can be administered through various routes such as inhalation, oral, transdermal, intravenous, intraperitoneal, and subcutaneous into the body and interact with the receptor proteins or cells.[111] It is reported that CNT is internalized into the cells and may lead to various toxicities related to cells or organs such as respiratory, liver, dermal, nervous, kidney, cardiovascular, and spleen.[111] These toxicities depend on the physicochemical characteristics of CNTs (such as type,[65,112] diameter,[65,112] structure, and length,[65,112,113]) solubilizing chemicals (PEG, SDS, and others.), functionalization of CNTs (such as covalent or non-covalent),[65] aggregation nature,[65,113] concentration and types of metal impurities (molybdenum, iron, cobalt, etc.),[65,112,113] method of preparation, doses of CNTs,[65,112,113] types of indicator dyes use to test cell viability and numerous kinds of cell could be enormously crucial in biological sensitivity to nanomaterials.[19,107] Smaller CNTs (less than 1 µm) easily penetrate cell membranes, whereas longer CNTs (more than 1 µm) cannot internalize into the cell and lead to biopersistence.[19,107] SWCNTs are less fibrous and hydrophobic (because hydroxyl and carboxyl groups exist) and have larger surface areas with more vital, more substantial van der Waals forces than MWCNTs. As a result, SWCNTs exhibit higher aberrant phagocytosis and less aggregation than MWCNTs. However, functionalization strategies can alleviate MWCNT aggregation.[19,107] Reportedly, the use of some natural dispersants (amylose, gum arabic, River natural organic matter, Suwannee), synthetic dispersants (Triton X-100, polyvinylpyrrolidone) and solubilizing agents (SDS) increases toxicity of SWCNTs whereas the use of DNA (π–π interaction) results in high solubility and stability in case of MWCNTs. Functionalized MWCNTs have enhanced solubility, improved dispersibility, reduced accumulation, and less toxicity than non-functionalized MWCNTs, whereas functionalized SWCNTs show higher toxicity than non-functionalized SWCNTs.[19,65] Impure CNTs (with metal impurities: molybdenum, nickel cobalt, copper, iron) increase the level of Cytokine (CD8+) compared to purified CNTs.[19,107] Shorter or tangled CNTs effectively eliminated via phagocytosis by the cells, whereas longer and rigid CNTs that cannot complete phagocytosis may cause cancer.[19,107] Various factors affect the toxicity of CNTs, as illustrated in **Figure 14**.

Cellular uptake and toxicity mechanisms such as apoptosis or necrosis were investigated by Benincasa et al., Yazdani et al., and He et al. as illustrated in **Figure 15**.

8. Future Perspective of CNTs in Therapeutic and Diagnostic of Fungal Infection

Diverse chemical strategies have generated CNT hybrid materials. These strategies include functionalizing CNTs with inorganic, organic, polymer, or bioactive components. The primary

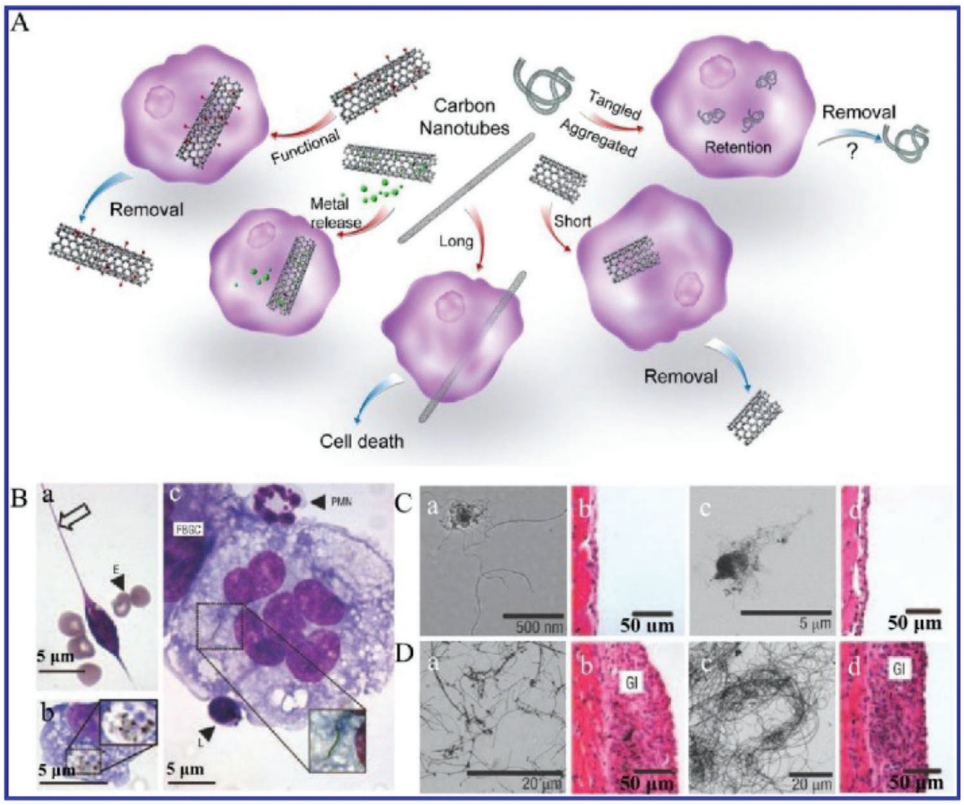

Figure 14. Illustrative image of various factors that influence internalization, distribution, and toxicity of CNTs; A) types of CNTs, B) giant cells (FBGCs) with internalized long, C) granuloma responded in mice by the exposure of long CNTs, D) granulomatous inflammation observed in mice by exposure of long CNTs. Reproduced with permission.[114] Copyright 2012, American Chemical Society.

goal of these modifications is to bestow qualities such as solubility, biocompatibility, and targeted interactions with the CNTs. These CNT Hybrid exhibit an apparent capacity for efficient cellular membrane traversal. They can be loaded with biologically active compounds, which are subsequently transported to the cell cytoplasm. The tunable chemistry of CNTs presents the opportunity to incorporate multiple functionalities onto a single nanotube, enabling concurrent utilization of targeting ligands, contrast agents, therapeutic drugs, and reporter molecules. CNT hybrids have been proven to have a high potential for delivering a wide range of antifungal agents such as AMB, NYS, FLC, and curcumin with increased efficiency, efficacy, biocompatibility, and therapeutic properties. Drug-loaded CNT hybrid and F-CNTs have shown solid antifungal activity, which will pique the curiosity of researchers as alternative NCs to deliver antifungal drugs for eradicating pathogenic fungal species. Their optical characteristics may also be used to diagnose fungal infection conditions. Villamizar et al. developed a CNT-based sensor for detecting fungal infections such as *Candida albicans*.[116] Chemical sensors based on CNT-HMs doped with nitrogen or boron can be used to distinguish between infected and uninfected sites.[117]

However, definitive clinical integration of CNTs requires further investigation with various precautionary steps considering their cytotoxicity and immunogenicity. Addressing the primary concern of long-term toxicity remains pivotal. While extensive in vitro and in vivo studies indicate non-toxicity of suitably F-CNTs to cells and mice, thorough investigations employing diverse animal models, varying dosages, and incubation durations are imperative. Achieving successful in vivo drug delivery with CNTs, despite promising in vitro demonstrations, remains a challenge. Optimal surface functionalization of CNTs for specific biomedical applications mandates special attention. Tailoring surface chemistry to mitigate toxicity and enhance specificity necessitates consideration of factors like nanotube structure (single-walled, double-walled, and multi-walled), length, aspect ratio, surface area, aggregation extent, oxidation degree, surface topography, bound functional groups, and fabrication methodologies.

The non-biodegradable nature of these nanomaterials presents a constraining factor. Nevertheless, indications of in vivo excretion imply plausible elimination following the fulfillment of their intended functionalities. The kinetics of CNT excretion, organ-specific distribution, and immune-modulatory responses will intricately shape their safety delineations and, subsequently, their viability for pharmaceutical advancement. Consequently, establishing metrics encompassing agglomeration magnitude, biodistribution kinetics, and elimination routes assumes pivotal significance in CNT-facilitated DDSs.

9. Conclusions

Various conventional and modern drug delivery approaches have been documented for potential significance in antifungal

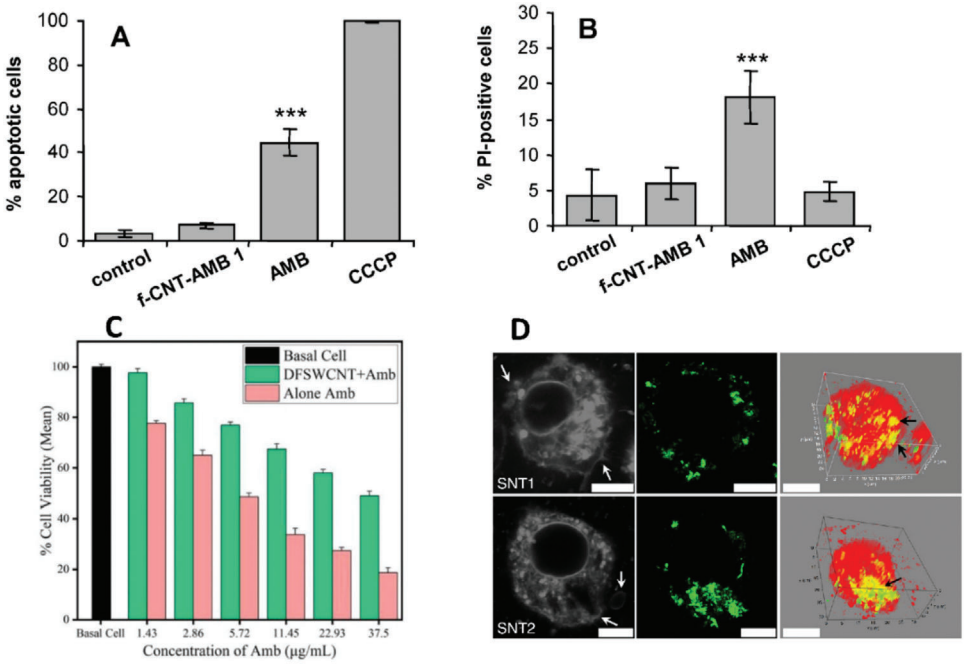

Figure 15. A) Percentage of cell apoptosis and B) after treatment with F-CNT/AMB (incubation for 16 h at 37 °C) analyzed by flow cytometry. Reproduced with permission.[87] Copyright 2011, American Chemical Society. C) Biocompatibility assays of AMB-loaded CNTs in HEK-293 cells (AMB drug concentrations ranging from 1.43 to 37.5 μg mL^{-1}). Reproduced (Adwith permission under the term of CC-BY license https://creativecommons.org/licenses/by-nc-nd/4.0/.107.[94] Copyright 2022, The Authors, published by Springer Nature. D) Confocal images of cells after treatment of CNTs lipid bilayer fluorescence, CNTs reflection, and 3D reconstruction by Imaris software (from left to right) and membrane wrinklesincated by white arrows. Reproduced with permission under the term of CC-BY license.[115] Copyright 2018, The Authors, published by Springer Nature.

drug delivery, including vesicular-based drug delivery vehicles, nanostructured lipid carriers, SLNPs, polymeric nanocarriers, nanoemulsions, metallic nanoparticles, and other nanocarriers. The shortcomings associated with conventional antifungal drug delivery can be circumvented using nanocarriers. Many strategies have been developed to render antifungal drugs bioavailability, biocompatibility, and bioactivity by integrating them into various nanocarriers, such as CNTs. Furthermore, recent literature has shown promising applications of CNTs, such as bioinks[118] that could be combined with printable silk fibroin matrix for précised organ printing.[119] Another to mention is the application of CNTs in microfluidics for advancing lab-on-chip technology by tailoring 1D to 3D closed architectures for the long-term harboring of cellular models.[120,121] Thus, with innumerable bio applications of CNTs, in this review, we have discussed deeper insights and advances gained on emerging CNT-based drug delivery strategies for efficient antifungal drug delivery to target sites in numerous mycosis treatments. Considering the dynamics of evolving pathogens affecting public health and intense research to counter these risks, this is the need of the hour.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

antifungal drugs, carbon nanotubes, drug delivery systems, functionalization, nanocarriers, pertinent antifungal therapeutics

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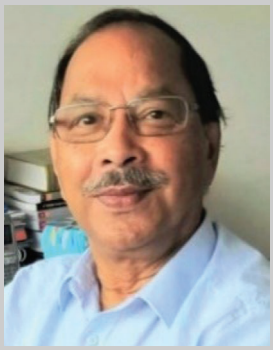

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