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COMPREHENSIVE REVIEW

Coumarins: antifungal effectiveness and future therapeutic scope

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Abstract

The antifungals that are in current clinical practice have a high occurrence of a side effect and multidrug resistance (MDR). Researchers across the globe are trying to develop a suitable antifungal that has minimum side effect as well as no MDR issues. Due to serious undesired effects connected with individual antifungals, it is now necessary to introduce novel and effective drugs having numerous potentials to regulate complex therapeutic targets of several fungal infections simultaneously. Thus, by taking a lead from this subject, synthesis of potent antifungals from coumarin moiety could contribute to the development of promising antifungal. Its resemblance and structural diversity make it possible to produce an auspicious antifungal candidate. Due to the natural origin of coumarin, its presence in diversity, and their broad spectrum of pharmacological activities, it secures an important place for the researcher to investigate and develop it as a promising antifungal in future. This manuscript discusses the bioavailability of coumarin (natural secondary metabolic molecule) that has privileged scaffold for many mycologists to develop it as a broad-spectrum antifungal against several opportunistic mycoses. As a result, several different kinds of coumarin derivatives were synthesized and their antifungal properties were evaluated. This review compiles various coumarin derivatives broadly investigated for antifungal activities to understand its current status and future therapeutic scope in antifungal therapy.

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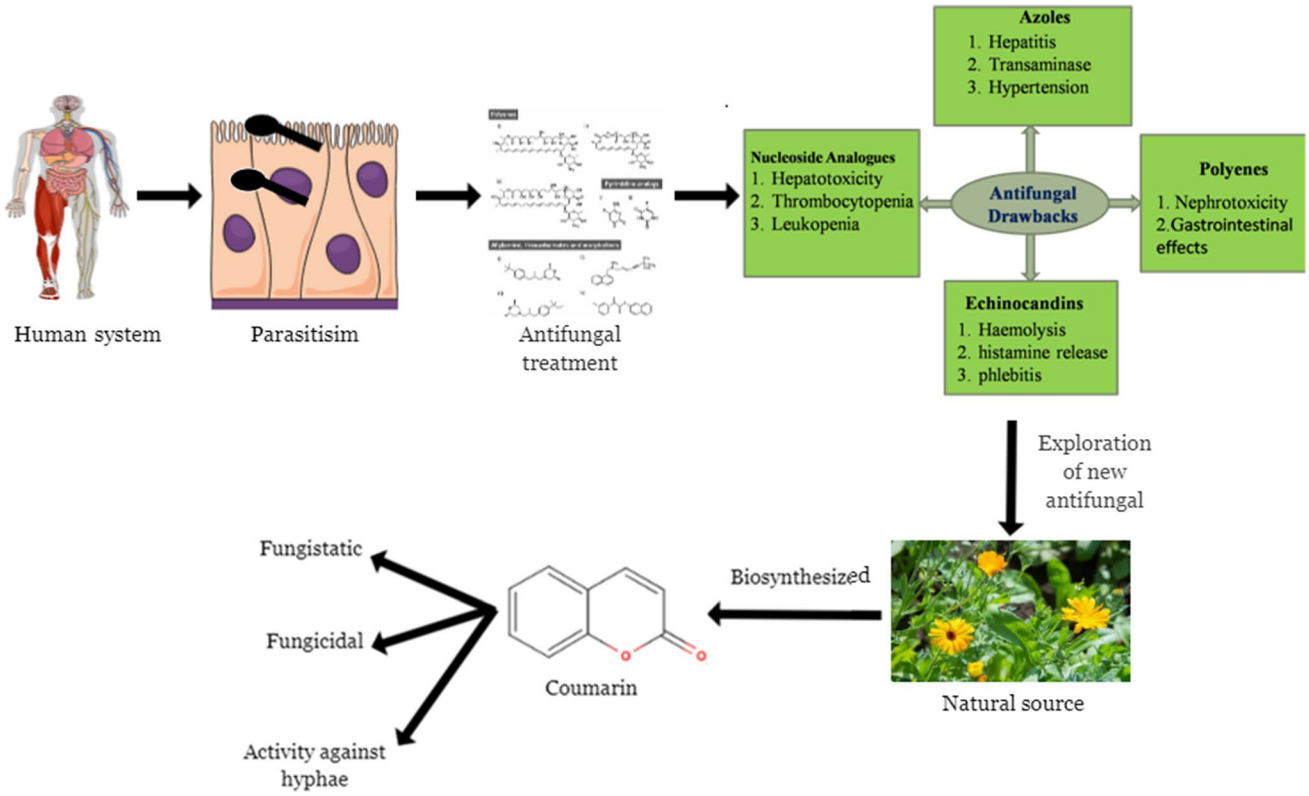
Graphic abstract



Keywords Coumarin · Structural diversity · Bioactivity · Promising antifungal

Introduction

Most of the severe fungal infections in human are caused by three main fungal species, i.e., *Candida, Cryptococcus,* and *Aspergillus* [1–4]. To establish fungal infection in host, there are four different criteria, i.e., pathogen (a) must be capable of reproducing at or above 37 °C, (b) must be able to enter into specific host tissue by diffusing host tissue barrier, (c) must be able to concentrate and engulf ingredients of human tissue, and (d) must be capable standing firm with the human immune system [5]. The coumarin (2*H*-1-benzopyran-2-one) was first isolated from a plant species *Coumarouna odorata.* It is a heterocompound known as benzopyrone containing benzene and α-pyrone rings. Mostly these compounds are distinguished in several families of plants, fungi, and bacteria [6, 7]. More than 1300 coumarin compounds were found, and several coumarin derivatives were synthesized as they have six different transposition sites available [8]. Based on in vivo experiments in rats, coumarins are banned from the food market by the Food and Drugs Administration (FDA), USA, in 1954 because it was producing hepatotoxicity in rats. The hepatotoxicity of coumarin is species-dependent and not toxic in other species like mice, hamsters, and gerbils [9]. Among all natural compounds, coumarins include a great assortment of bioactivities containing anticoagulant, estrogenic, dermal photosensitizing, antimicrobial, vasodilator, molluscicidal, anthelmintic, sedative, hypnotic, analgesic, and hypothermic activities [10–12]. In addition to these properties, coumarin compounds are also used as cosmetics and additives in food products (due to its sweet flavor) [13]. From *Cyperus incompletus,* different kinds of coumarins are isolated and purified and its antifungal assays demonstrated that it has essential actions against fungus due to an extra oxygenated functional group and/or an aromatic hydroxyl group (ether and ester) in 6 and 7 positions of coumarin [14]. This review describes coumarin and its derivatives as a promising antifungal moiety. We have discussed human fungal pathogens, their pathogenicity, mechanism of fungal parasitism, drawbacks of available antifungals, antifungal activity of coumarins, and its derivatives for its possible development of antifungal having multiple-drug-targeting potential.

Human fungal pathogens

In humans, mostly fungal infections arise from the epidermal part of the skin or mucosal surface, and then, infection becomes invasive to the internal organs. Though superficial infections are easy to diagnose, the incidence and severity of internal infections (interior structural and functional unit of a human) are high. Immunodeficient persons with HIV/AIDS, autoimmune disease patients, and patients under organ transplantation and chemotherapy treatment are always under high threat from fungal infection [15]. Among 1.5–5.0 million species of fungus on the universe [16], only few hundred fungal species are the causal agent of a disease in human beings and very limited are able to infect the healthy people [17]. In immunocompromised patients, the causal agent of fungal infection is *C. albicans*, *C. neoformans*, *A. fumigatus*, *H. capsulatum*, etc. in which *C. albicans* survive within the host acting as commensalism, and later on, *C. albicans* becomes an opportunistic organism for fungal infections [18]. Some diseases caused by these fungi are aspergillosis, coccidioidomycosis, candidosis, cryptococcosis, mycetomas, histoplasmosis, mucormycosis, and paracoccidioidomycosis. These diseases are very devastating to human beings if they are not diagnosed properly [19]. In the host, these fungi create allergic reactions to fungal proteins or toxic reactions of fungal toxins and ultimately fungus establish superficial, cutaneous, subcutaneous, or systemic infections [20].

Cutaneous fungal pathogen

Normally fungal colonization occurs in different body parts of humans with unique physiological and immunological niche by the exposed interface to the outside which provides optimized incubation period like moisture, nutrients, and temperature for the development of suitable microorganism even in healthy people [21, 22]. The cutaneous microbiota is associated with the dermis and pilosebaceous unit of the hair follicle. They are recognized as dermatophytes which are the causal agent of skin mycoses [23–25]. The fungal infections are also persistent in epidermis and nails and affect 20–25% of the universe population. The spectrum of superficial infection depends on the geographical area and location, and some opportunistic species like *Microsporum canis*, *T. violaceum*, *M. audouinii*, *T. soudanense,* and *T. tonsurans* [26] were reported. Several microorganisms are an essential part of the host–microbiota system, and they survive unaggressively with their host (e.g., *C. albicans* and *S. aureus*) and causes cutaneous infection [27, 28]. The cutaneous infection was mostly caused by species of *Candida* like *C. orthopsilosis*, *C. tropicalis*, *C. parapsilosis*, and *C. albicans* [29, 30]. Thickening of the epidermis, hyperkeratosis, and erythema are a habitual indication of cutaneous candidiasis [31]. In fact, superficial infection is encountered by some *Alternaria spp.* and causes cutaneous and subcutaneous alternariosis [32–34]. Cutaneous fungal infection in neonates shows a high jeopardize because of the maturation of skin after the first few weeks to months of life by the keratinization process. However, the epidermis avoids the loss of water and allows a barrier to invasion by opportunistic fungus [35–38].

Mucocutaneous fungal pathogen

Due to the poor clinical setup and unavailability of advanced therapy and antifungal resistance, fungal infection becomes very grievous to our society. Due to its pathogenicity, mucosal-acquired fungal infections have high susceptibility and mortality. The number of mucocutaneous infections is seen in universe in immune-suppressed patients [39]. The chronic mucocutaneous candidiasis syndrome (multiple superficial sites particularly mouth, epidermis, and finger nails) is the most frequent type of infection caused by opportunistic dermatophytes candida by colonizing the various mucosal barriers like the esophagus, genitourinary tract, and oral cavity [40, 41]. The mucocutaneous candidiasis occurs to individuals symbiotically and damages the mucosal barrier by secreting numerous factors (toxins and hydrolytic enzymes) and acquiring nutrients [42].

Systemic fungal pathogen

In the case of human tissue, the invasion of the total body part demonstrates systemic fungal infection and shows initial infection, histoplasmosis, and coccidioidomycosis. Generally, the etiology of systemic fungal infection is of two types: (a) endemic mycoses (caused by dimorphic fungi like *Blastomyces dermatitidis*, *Histoplasma duboisii*, *Coccidioides immitis*, *Penicillium marneffei*, and *Sporothrix schenckii*) and (b) opportunistic mycoses (caused by *Candida, Aspergillus, Cryptococcus,* and Zygomycetes) [43–46]. However, *C. albicans* is a highly opportunistic pathogen causing the nosocomial fungal infections and they are growing in the number of immunocompromised patients isolated from intensive care unit (ICU) [47].

Pathogenicity of the fungal pathogen

The name pathogenesis comes from two Greek words, i.e., "pathos" means disease and "genesis" means development. A fungus which is responsible for causing disease in the host is known as a pathogenic fungus [48]. A human pathogenic fungus has the capability to invade the human tissue mostly in immunocompromised person and generate a life-threatening disorder via expressing some virulent factors

(Table 1). However, the contribution of specific genes and their respective products (proteins) shows tissue invasions in the individuals [48, 49]. Furthermore, several characters such as expression of adhesion molecule, morphological dimorphism, alternation of phenotypic character, producing biofilm, and secretion of several hydrolytic enzymes are deliberate in virulence [50]. Usually, for the pathogenicity, the elongated hyphae or pseudohyphae of fungi plays a significant role in the deep incision of tissue [51].

Mechanism of parasitism

During the host-mycoses interrelationship, a cross-talk mechanism reveals the systemic infection. The biological interpretation in a host–pathogen interaction involves several crucial steps like (a) attachment to host membrane followed by multiplication, (b) tissue invasion of the host, and (c) dissemination [52].

Adherence and proliferation

In the initial step of pathogenicity, yeast budding cells adapt the epidermal part of the host and believe to be a primary virulence factor. Most neonates become a suitable substrate for several fungal pathogens during the gestation period and colonize into the gastrointestinal tract as well as the oral cavity of an infant [51, 53]. The adherence of pathogen to the superficial part of the individual provides particular adhesins present in fungal cells to determine ligands such as fibronectin, proteins, and fibrinogen [54]. Mostly fungal pathogens are attached to the host epithelial cell, and they are immediately taken up by the epithelial cells [55]. For the multiplication and formation of hyphal and/or pseudohyphae, fungus required a suitable environmental niche in the host [56]. For the survival of pathogen at various types of niche in host tissue, the propagation of pathogen is able to accommodate with huge alternation of host environmental pH of different tissue sites and maintains its virulence. They regulate some cell signaling pathways which are involved in the pH of the host environment [57, 58].

Tissue invasion and dissemination

The contagious disease is caused by several mycoses in the human by manipulating host immune response. A number of pathogenic fungal cells get entered into mammalian cells and manipulate the mammalian immune system. The process of evading host cell (both phagocytic and non-phagocytic cells) allows the pathogen to travel across the cell membrane. Several opportunistic fungal species enter into the host cells either in vitro or in vivo, but the invasion process is described for some fewer species [59–63]. Invasion of pulmonary epithelial and endothelial cells by pathogen gains the profit for mycoses, and mostly the internalization of mammalian tissue become a nutrient source for their survival [64]. The most common fungal infections—aspergillosis and candidiasis—are induced by two fungi: *C. albicans* and *A. fumigatus* that exert few initial processes in which they can move from one cellular environment to another environment inside the mammalian body. The primary mechanism is to induce endocytosis in which the specific fungal proteins are deposited on the cell surface which interferes with host ligand binding, thereby initializing the engulfment of fungal hyphae by the mammalian cell. The secondary mechanism is the active penetration of fungal viable cell into the host cell. The evidence showed the process of active penetration mediated by significant enzyme SAPs (secreting aspartic proteases) [65–69]. Pathogenic fungus like *C. neoformans* disseminates from lungs through the induced endocytosis, but *C. neoformans* have substitute pathway of translocating from an individual cell. They have capable of altering the host cell environment and germinate until the breaking of host tissue and ejected from the tissue through exocytosis [70, 71].

Table 1 Several types of mycosis with respect to their associated problems

Infectious agent	Associated problems	Process of infection	References
Aspergillus spp.	Aspergillosis	Invasive	[62]
Candida spp.	Candidiasis	Superficial and systemic	[68, 69]
C. neoformans	Cryptococcosis	Invasive	[70, 71]
Rhizopus spp., *Mucor* spp., and *Absidia* spp.	Zygomycosis	Cutaneous	[53, 183]
B. dermatitis	Blastomycosis	Subcutaneous and systemic	[184, 185]
H. capsulatum	Histoplasmosis	Systemic	[186]

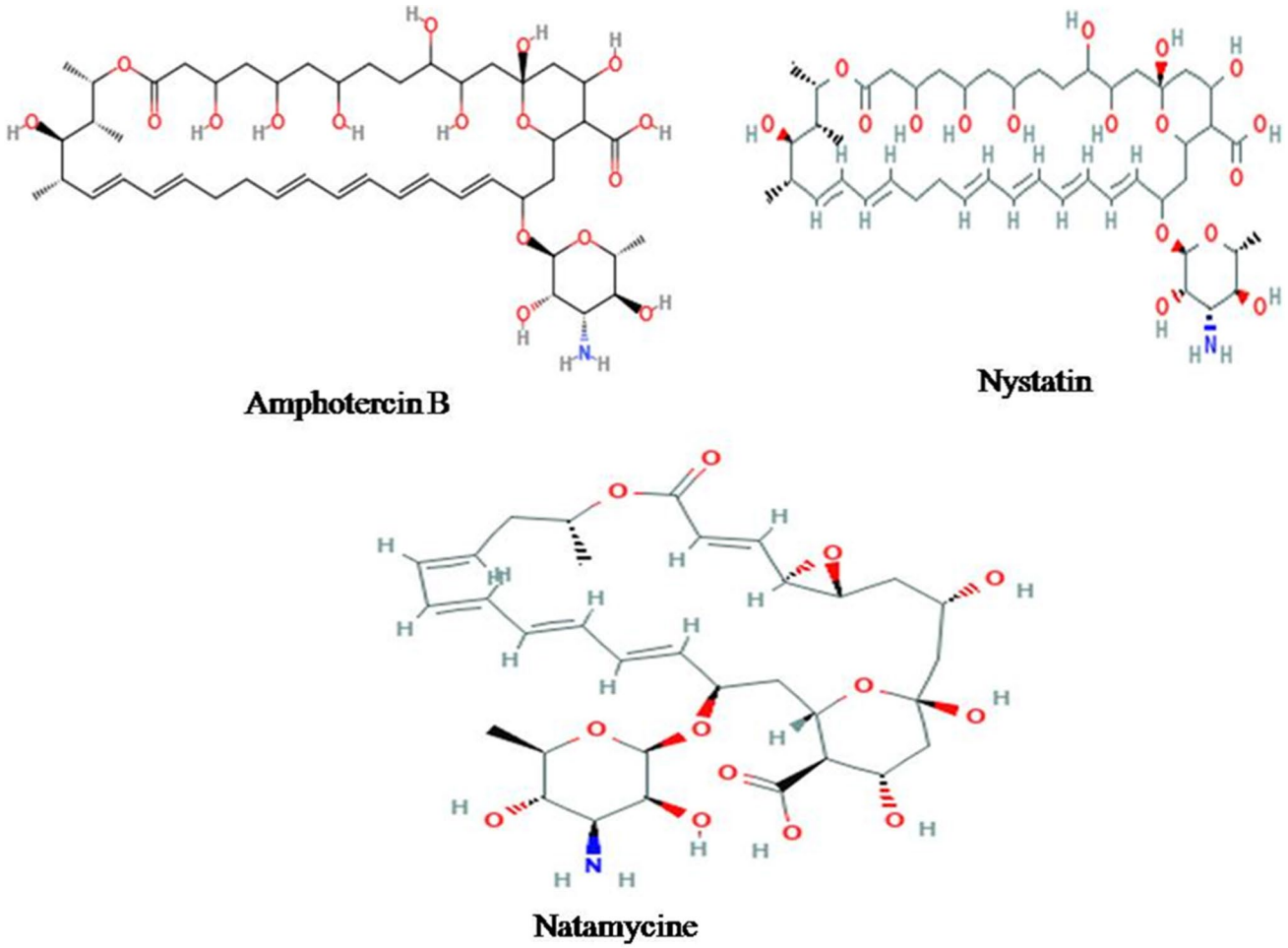


Fig. 1 Structure of a few effective antifungal marketed drugs

Available antifungal drugs: mechanism and drawbacks

For the diagnosis of cutaneous, mucocutaneous, and systemic mycoses, there are few antifungal drugs available (Fig. 1) which can target/inhibit the fungal infection [20]. Consequently, this antimycotic agent demonstrated a change in the pattern of differentiation, transformation, growth, and viability of mycosis (Table 2). We have briefly discussed the pros and cons of existing antifungals below.

Azole group of antifungals

The azole group of antifungals is the synthetic mycotic agent first reported for the diagnosis of systemic and mucocutaneous dermatophytes in early 1960s [72, 73]. The five-membered heterocyclic structure imidazole shows their broad-spectrum antifungal activities based on the organic synthesis of the new compound through modification of the molecular structure. For instance, pyrazoles are most significant heterocyclic compounds that can be selectively lithiated at different carbons and afterward react with an electrophile to show antifungal properties [74–77]. The action of these azole groups of antifungals inhibits the addition of methylated sterols and demolishes the mixture of the lipid bilayer. At higher concentration of azole group of antifungals, few imidazoles exert direct inhibitory action upon dynamic nature of membrane without interfering with sterols and sterol esters [78–80]. Recently synthesized benzimidazole salts were tested for their inhibitory property against *C. albicans* and *A. fumigates* which reveals that reduction in population and also these derived salts are used as an inhibitor against acetylcholine esterase and carbonic esterase of fungus [81–84]. Depending upon the presence of nitrogen group (miconazole, voriconazole, itraconazole, terconazole, posaconazole, and fluconazole) in five-membered azole ring, antifungal azoles are sorted as triazoles and imidazole and mostly used against filamentous fungi and yeast. For the reduction in mycotic growth, azole drugs first attack the ergosterol biosynthetic pathway [72, 85, 86]. This

Table 2 Category, target, and drawbacks of some marketed antifungals

Category	Drugs	Infection type	Possible target	Draw backs	References
Azole	Ketoconazole	Candidiasis, coccidioidomycosis, blastomycosis, histoplasmosis, paracoccidioidomycosis, and dermatophytosis	Suppress cytochrome P450-dependent enzyme in the cell membrane	Fatal toxic hepatitis	[156, 157]
	Voriconazole	Aspergillosis, fusariosis, scedosporiosis, candidiasis		Skin rash, transaminase elevation	[158–160]
	Posaconazole	Prophylaxis for aspergillosis and candidiasis		Vomiting, diarrhea, transaminase elevation, nausea, hyperbilirubinemia	[161–164]
	Itraconazole	Aspergillosis, blastomycosis, histoplasmosis, sporotrichosis		Hepatitis, hypokalemia, hypertension, heart failure	[80, 164, 165]
	Fluconazole	Vaginal candidiasis, cryptococcosis, mucosal and systemic candidiasis,		Hepatic necrosis, alopecia, anaphylaxis	[166, 167]
Polyene	Amphotericin B	Most type of fungal infections	Binding to ergosterol leads to fungal cell membrane leakage	Nephrotoxicity, decreased blood potassium	[167, 168]
	Nystatin	Oropharyngeal candidiasis		Gastrointestinal effects, nausea, vomiting	[169]
	Natamycin	Aspergillosis, fusariosis			[170]
Echinocandins	Caspofungin Micafungin Anidulafungin	Esophagal candidiasis, oropharyngeal candidiasis, invasive aspergillosis, and candidemia	Inhibit the β(1,3)-glucan synthase disturb the cell wall rigidity	Hemolysis, phlebitis, histamine release, fever, liver toxic effects	[97]
Nucleoside analogs	5-Fluorocytosine	Cryptococcosis candidiasis	Disrupt the fungal protein synthesis	Hepatotoxicity, leukopenia, and thrombocytopenia	[171]
Others	Allylamine	Fungal nail infections, candidiasis, dermatophytosis	Inhibit the sterol synthesis by targeting the squalene epoxidase	Gastrointestinal upset, nausea	[104, 172]
	Morpholine	Dermatophytosis, vaginal candidiasis	Interference with D14 reductase and D7-D8 reductase	Not available	[173, 174]

drug inhibits the synthesis of a lanosterol-14α-demethylase enzyme in dermatophytes [87]. Besides *Pythium* spp. and *Pneumocystis* spp., the *ERG11* gene is responsible for 14α-demethylase enzyme (under cytochrome P450 enzymes) production in all mycoses involved in secretion of ergosterol which is required for cell membrane formation. The blocking of 14α-demethylase enzyme reveals the disturbances in cell membrane rigidity, formation chitin, cell membrane permeability, and nutrient transport channel [88, 89].

Polyene group of antifungals

The most opportunistic genus of *Streptomyces* bacteria produces broad-spectrum antifungal drugs such as polyenes (nystatin, amphotericin B, natamycin) by fermentation and now taken as topical drugs [90]. The first antifungal drug nystatin was biosynthesized in *Streptomyces noursei* at the Division of Laboratories and Research, New York State Department of Health [91]. Nystatin is more toxic for human cells in in vitro as well as in vivo experiments. So, mostly in systemic infection diagnosis is made intravenously [92]. Like the structure of macrolides, polyenes have also both properties of hydrophilicity and hydrophobicity. Generally, the composition of polyene is 20–40 cyclic rings coupled with the d-mycosamine group. The existence of amphiphilic properties of polyene is due to the availability of double bonds, saturated and unsaturated carbon atom, and few hydroxyl groups on their respective terminal sides [93]. Fungal cell membrane plays an important role in cell survivability by maintaining their integrity. The accumulation of polyene targets ergosterol (an integral part of the cell membrane) and creates pores in the membrane of fungus that results in exhaustion of all cellular components and the release of cytoplasmic content [94]. Nephrotoxicity is a major drawback by taking amphotericin B due to its affinity toward sterol compound (cholesterol presence in mammals) [95].

Echinocandin group of antifungals

Echinocandins are a modern antifungal agent because it has few side effects due to their less toxicity and nephrotoxicity in comparison with other antifungals. The first echinocandin—cilofungin—was discovered for the treatment of most fungal infection, but after the experimental analysis of cilofungin exposed its toxicity, this drug was avoided [96]. After that, some novel echinocandins (i.e., caspofungin, micafungin, and anidulafungin) were developed that presented their high incidence of clinical development in the twentieth century and approved by the FDA and USA and also followed by European Agency. Echinocandins are large semisynthetic lipopeptide compound having amphiphilic cyclic hexapeptide with N-linked long fatty acid chain [90, 97]. In most of the mycoses, β(1-3)-glucan synthase catalyzes the polymerization of uridine diphosphate glucose to β(1-3)-glucan which was treated as one of the most important structural components for the protection of fungal cell wall. However, the echinocandin group of antifungal drugs blocks the synthesis of β(1-3)-glucan by breaking the cell wall and leads to the cell wall destabilization [98, 99]. Since this group of antifungal drugs has high molecular weight and gets assimilated into the gastrointestinal tract, therefore, this kind of drugs is given via a vein [100].

Nucleoside analogs group of antifungals

5-Fluorocytosine is a cytosine derivative first introduced in 1957. Cytosine permeases are enzyme selectively transmit 5-fluorocytosine through the cell wall of few fungi. These drugs stop the DNA synthesis by targeting 5-fluorouracil and then exchanged with 5-fluorodeoxyuridine monophosphate by the process of phosphorylation [101]. For further enhancement of the drugable property, 5-fluorodeoxyuridine monophosphate can be re-phosphorylated which interferes with protein synthesis inhibition [102].

Other group of antifungals

Squalene epoxidase is the most common enzyme involved in the biosynthesis of ergosterol in most of the fungi. Accumulation of both thiocarbamate and allylamine groups of antifungal agent suppresses the squalene epoxidase leading into the depletion of ergosterol level [103]. The most commonly available allylamine drugs for therapeutic purpose are terbinafine and naftifine [104]. Morpholines is a fungicidal drug that represses expression of *ERG2* and *ERG24* gene catalyzes to sterol D14 reductase and D7-D8 reductase, respectively [105, 106].

Coumarin and its derivatives

Coumarin is a secondary metabolite of phenolic substances found in the plants and exhibits a wide range of antimicrobial activities [107, 108]. The presence coumarin moiety is found mostly in the plants of *Guttiferae*, *Oleaceae*, *Apiaceae*, *Umbelliferae*, *Caprifoliaceae*, *Clusiaceae*, *Rutaceae,* and *Nyctaginaceae* families [109]. The first coumarin was synthesized by following the mechanism of the Perkin reaction between salicylaldehyde and acetic anhydride in nineteenth century (Fig. 2) [110]. These heterocyclic phenolic substances (coumarin) have diverse activity like antiinflammatory [111], anticoagulant [112], antibacterial [113], antifungal [114], antiviral [115], antihypertensive [116], antitubercular [117], anticonvulsant [118], and antioxidant [119]. Four different types of coumarin are categorized

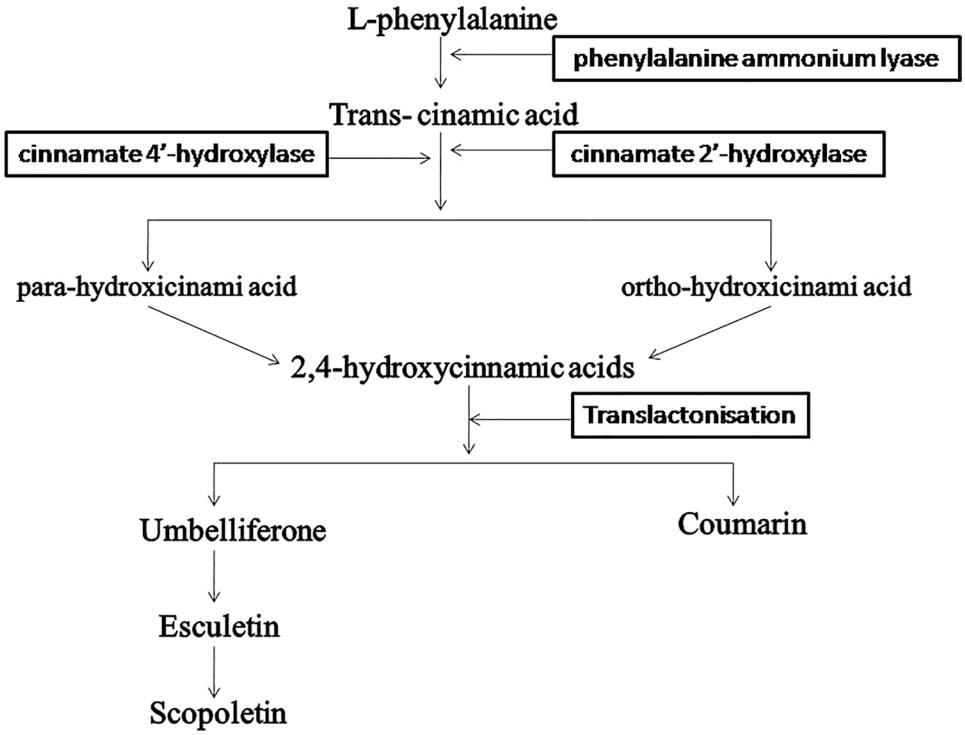


Fig. 2 Biosynthetic pathway of coumarin

according to their structure, i.e., the simple coumarins, furanocoumarins, pyranocoumarins and the pyrone-substituted coumarins [120, 121]. All the subclasses of coumarins are obtained by the biosynthesis of coumarin through the shikimic acid pathway. This coumarin biosynthesis is only possible by yielding umbelliferone compound via cinnamic acid through a metabolic pathway of phenylamine. In this process, phenylalanine ammonium lyase is an enzyme that deaminates the L-phenylalanine by generating trans-cinnamic acid (Fig. 2). The process involves the production of 2,4-hydroxycinnamic acid by two important catalysts such as cinnamate 2′-hydroxylase and cinnamate 4′-hydroxylase through hydroxylation of trans-cinnamic acid. To produce novel coumarins (umbelliferone, esculetin, and scopoletin), prominent chain isomerization and consequent lactonization processes were used [121, 122]. Not only is biosynthesis of coumarin confined to the plants, but also several microorganisms like fungi and bacteria have a specific metabolic pathway to biosynthesize coumarin compound [123].

The coumarins have a simple structure, and its versatility makes it very significant for broad-spectrum application [124] such as in agrochemical [125], pharmaceuticals [126], cosmetic industry [127], fragrance industry [128], and food industries [129]. Due to a wide range of biological activities, coumarins show very significant activity in combinatorial library synthesis [130]. Table 3 elucidates the synthesis and biological behavior of coumarin derivative compound. Also, the substituent of the coumarin utilizes for the diagnosis of degenerative brain disorders like Parkinson's and Alzheimer diseases by blocking cholinesterase [131, 132]. Several other methods were also developed for the synthesis of coumarins like Pechmann reaction [133], Knoevenagel condensation [134], Witting reaction [135], and Claisen rearrangement [136] using comprehensive chemical agents like P_2O_5, H_2SO_4, ionic liquids, $HCLO_4$, and catalyst [137–142].

Antifungal activity of coumarins

The predominant application of available antifungal agent leads to the resistance of endangered dermatophytes. Also, the majority of the resistance mechanisms have elucidated at the molecular level for the fungal pathogens. So it is now developing to discover novel antifungal agent which achieves better therapeutic efficacy against pathogenic fungus [143]. Coumarin and its derivatives showed extensive pharmacological activity and considered as an antimicrobial agent due to its lower degree of cytotoxicity, less cost, and wide availability as a secondary metabolite in many plants [107, 108, 144].

Fungistatic activity

Mercer et al. suggested the introduction of water-soluble coumarin glycosides that have a tendency to convert inactive to an active drug by secreting β-glucosidase in mycoses. It hydrolyzes the pro-drug via producing potential antifungal aglycones like esculetin and fraxetin [145].

Table 3 A list of prominent coumarin derivatives having their structure, source, and antimicrobial activity

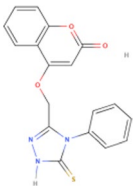
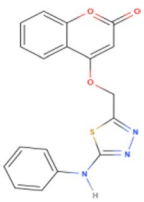
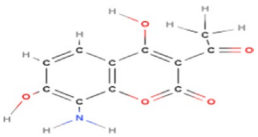
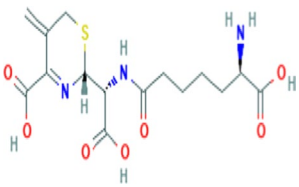
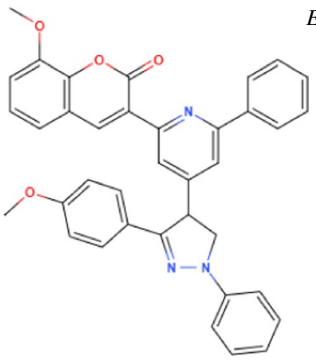
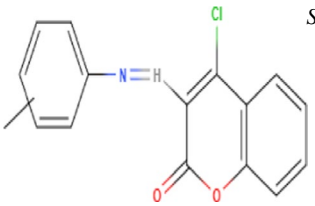
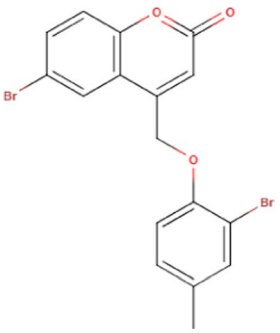
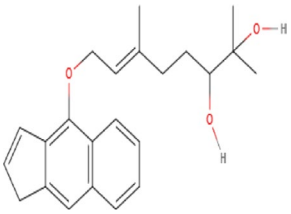
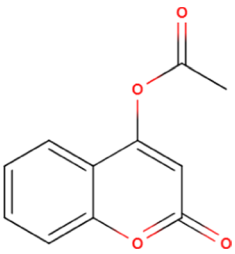
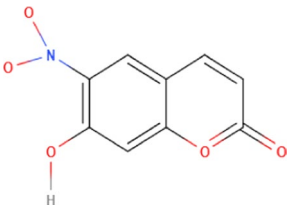
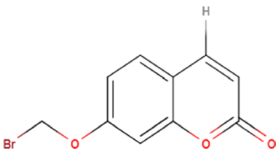
Coumarin derivative	Structure	Microorganism	Antimicrobial activity	References
4-((5-Mercapto-4-phenyl-4*H*-1,2,4-triazol-3-yl)-methoxy)-2*H*-chromen-2-one		*Aspergillus niger* and *Candida albicans*	Antifungal activity	[175]
4-((5-(Phenylamino)-1,3,4-thiadiazol-2-yl)methoxy)-2*H*-chromen-2-one		*Aspergillus niger* and *Candida albicans*	Antifungal activity	[175]
3-Acetyl-8-amino-4,7-dihydroxy-chromen-2-one		*Staphylococcus aureus*, *E. coli*, and *Bacillus cereus*	Antibacterial activity	[176]
Cephalosporin		*Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa*	Antibacterial activity	[177]
4-Methyl-3-phenyl-6-[4-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-6-aryl-pyridin-2-yl		*Escherichia coli, Bacillus subtilis*	Antibacterial activity	[178]
4-Chloro-3-((substituted phenylamino) methyl)-2*H*-chromen-2-one		*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Aspergillus niger, and Candida albicans*	Antibacterial and antifungal activity	[179]
4-Aryloxmethylcoumarins		*Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Aspergillus flavus, Aspergillus fumigates, Candida albicans, Penicillium notatum, Rhizopus*	Antibacterial and antifungal activity	[180]

Table 3 (continued)

Coumarin derivative	Structure	Microorganism	Antimicrobial activity	References
6′,7′-Dihydroxybergamottin		*S. aureus, S. epidermidis, P. aeruginosa, E. cloacae, K. pneumonia, and E. coli*	Antibacterial activity	[181]
4-Acetatecoumarin		*A. fumigates, A. flavus*	Antifungal activity	[146]
7-Hydroxy-6-nitro-2*H*-1-benzopyran-2-one		*A. fumigates* and *A. flavus*	Antifungal activity	[155]
7-(2-Bromoethoxy)-2*H*-chromen-2-one		*E. coli* and *M. albicans*	Antibacterial activity	[182]

Guerra et al. demonstrate that a novel coumarin derivative 4-acetatecoumarin represents the subsequent reduction in hyphal formation, as well as spore formation in *Aspergillus* spp. During conglomeration with azole group antifungals, it gave the evidence for inhibition of fungal growth [146]. Puttaraju et al. synthesized novel coumarin derivative by microwave irradiation method. One coumarin compound dihydrobenzo[4,5]imidazo[1,2-α] pyrimidine-4-one showed an exhibition of effective antifungal activity against *C. albicans, A. niger, A. fumigatus, A. flavus, F. oxysporum, P. chrysogenum* [147]. Marcondes et al. isolated mammeisin from Kielmeyera elata species of plant and tested its antifungal activity against various *Candida spp.* They detected that antifungal drug mammeisin demonstrates good activity for *C. tropicalis* as compared to fluconazole [148]. Umbelliferone, herniarin, scopoletin, and xanthotoxin were isolated from few herbal plants (originated in Finland) and examined its fungistatic activity against F*usarium culmorum*. The antifungal activity of these coumarins indicated that the rate of growth of *F. culmorum* was suppressed vigorously [149].

Fungicidal activity

Thati et al. describe the mechanism of action of some coumarin derivatives like 7-hydroxycoumarin-3-carboxylatosilver(I), 6-hydroxycoumarin-3-carboxylatosilver(I), and 4-oxy-3-nitrocoumarinbis(1,10-phenanthroline) silver(I) against an opportunistic yeast *C. albicans* and observe the death of *C. albicans*. Application of these potent coumarin derivatives reduced the efficacy of respiration system due to breakage of cytochrome synthesis in mitochondria, lower synthesis of ergosterol, and cell death by induction of apoptosis, and these are the manifestation for strong fungicidal activity [150]. Also, the antifungal activity of naturally occurring coumarin derivative osthole was considered as a potent antifungal drug due to its direct effect on cell wall modification and disruption of organelles that leads to the death of *Sphaerotheca fuliginea* [114]. Four osthole derivatives such as 7-allyloxy-3-methyl-4-oxo-4*H*-furo[3,2-c]chromene-2-carboxylic acid methyl ester, 2-acetyl-7-methoxy-furo[3,2-c]chromen-4-one, 7-methoxy-3-phenyl-furo[3,2-c]chromen-4-one, and 7-allyloxy-3-phenyl-furo[3,2-c]chromen-4-one were derived through

microwave-assisted protocol by Zhang et al. Among these coumarin derivatives, the EC_{50} value of compound 7-allyloxy-3-methyl-4-oxo-4*H*-furo[3,2-c]chromene-2-carboxylic acid methyl ester showed better fungicidal activity rather than a standard antifungal drug. Azoxystrobin showed strong activity against common plant fungal pathogens, i.e., *Rhizoctorzia solani, Colletotrichum capsici*, and *Botrytis cinerea* [151]. Siddiqui et al. synthesize novel 4-hydroxycoumarin derivatives, i.e., 1-(4-oxo-4H-1-benzopyran-3-yl)-1,1-bis(4-hydroxy-1-benzopyran-2-one-3-yl)methane that indicated a good fungicidal activity against pathogenic fungi *T. mentagrophytes, P. marneffei, A. fumigates,* and *C. albicans* [152].

Activity against fungal hyphae

Dietrich and Valio reported the biological activities of coumarin and its derivatives against various taxonomies of fungi such as *Phycomycetes, Ascomycetes*, and *Basidiomycetes* [153]. They showed predominant inhibition of mycelial growth at a constant concentration of coumarin. Knypl (*1963*) reported that coumarin at a higher concentration showed suppression of spore maturation in case of *A. niger* [154]. For the inhibition of mycelia development and conidia formation in *Aspergillus spp.*, Guerra and his collogues showed the strong antifungal activity of coumarin derivative 7-hydroxy-6-nitro-2*H*-1-benzopyran-2-one [155].

Future prospective

This review emphasizes that coumarin and its derivatives have significant antifungal efficacy against most threatened and opportunistic mycoses. The pharmacological assays of coumarin-based organic compound manifested that the antifungal activity of these derivatives was magnificent and could be a futuristic promising antifungal candidate. Although several pharmacological properties have been established for the bioactivity of coumarin and its derivatives, further one-step analysis of coumarin against fungal biofilm remains unexplored.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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