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Review

Plant bioactive molecules bearing glycosides as lead compounds for the treatment of fungal infection: A review

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ABSTRACT

Despite therapeutic advancement in the treatment of fungal infections, morbidity and mortality caused by these infections are still very high. There are approximately 300 fungal species that are infectious and can cause a variety of diseases. At present, several synthetic antifungal drugs are in clinical practice, many of them, however, are vulnerable to multidrug-resistant strains of microbes, and thus compromising the overall treatment outcomes. Glycosides are naturally occurring plant secondary metabolites with important therapeutic potential and clinical utility. The aim of this review was to focus on the antifungal effects of glycosides in preclinical studies with possible mechanism(s) wherein described. Published research show significant susceptibility of different fungi towards phytoglycosides, mediated through multiple mechanisms. Further detailed studies are needed to explain the clinical applications and limitations of these glycosides.

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Contents

1. Introduction

The risk of opportunistic mycotic infections in immunocompromised patients, such as those affected from cancer chemotherapy, human immunodeficiency virus, and organ transplantation has increased in recent years [1]. The fungus which mostly causes these infections in immunocompromised patients is *Candida albicans*, where 90% of *candidal vaginitis* in these patients and

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healthy women is caused by this strain [2]. Although there are great advances in drugs against mycotic infections, however, their usage is limited due to side effects associated with these drugs, in addition to the fact that *Candida* is becoming increasingly resistant to antifungal medications [3]. The antifungal drug amphotericin B, described as the 'gold standard' is widely used to treat serious fungal infections, however, this drug may cause nephrotoxicity and infusion-related reactions [4,5]. In addition, azoles antifungal drugs produce resistant strains of *Candida* species. Moreover, investigations undertaken by a number of researchers revealed that isolates taken from women affected by *Candidal vaginitis* are 3.6–7.2% resistant to fluconazole [6].

Surveys conducted in USA claimed that approximately 2 million people suffer from fungal and bacterial infections each year, and that 65% of patients acquire resistance to one of the drugs [7]. Continuous treatment and repetitive usage of antibiotics, in addition to unsatisfactory control over infections, have led to cases of drug treatment failure in fungal infections [8]. Due to these problems and others, research in the field of anti-infective therapies, and the search for alternatives are becoming a necessity [9,10].

Natural products have shown great promise in the discovery of new antifungals. The recent example is enfumafungin, a triterpene glycoside isolated from endophytic *hormonema* species [11] and is a potential clinical candidate along with more potent derivative [12]. Plants are rich sources of antimicrobial agents and have been utilized for centuries in folk medicine to treat microbial infections [13,14]. Furthermore, plant products used in traditional medicines are mostly safer and may possess better disease controlling capabilities as compared to synthetic drugs probably owing to diverse chemistry [15–18]. Several recently published reviews suggest that different infectious and life-threatening diseases have been effectively treated with herbal medicines [19,20]. Owing to their abundant availability and diversity, natural products such as plant extracts or pure herbal medicines provide opportunities for the discovery of new drugs [18,21,22]. As new infectious diseases are emerging, there is a need to discover and produce new antimicrobial agents with new mechanisms and assorted chemical structure which are safe, efficacious, and economical [23].

2. Antifungal resistance

In recent times, antifungal resistance is a global medical challenge for practicing physician and the number of infections increasing drastically due to compressed immune system [24–27]. There are a number of molecular mechanisms proposed for antifungal resistance caused by genetic modification. As a result of resistance to common antifungal, millions of people die from various types of fungal infection all over the world and the mortality rate is comparable to tuberculosis or malaria [28]. The systemic mycoses have commonly been observed in patients with severely impaired immune systems, people with organ or bone marrow transplants, cancer patients undergoing chemotherapy or in intensive care unit patients, as well as both neonates and the elderly. Focus on novel strategies to block the emergence of drug resistance and render resistant pathogens responsive to antifungals will be critical to treating life-threatening fungal infections. To encounter all these unavoidable situations, adaptation of novel strategies are highly required to improved the efficacy and safety and thus patient compliance [29–31]. For this purpose, several sources are used to designed more effective molecules with better tolerability against resistance by using modern drug delivery system [32–35].

3. Glycosides as therapeutic agents

Glycosides are compounds in which a sugar molecule is attached, via a glycosidic linkage, to the anomeric carbon of a non-sugar moiety. Certain enzymes present in the body can activate some of glycosides through hydrolysis, by removing its sugar molecule. These activated molecules can then act on specific targets, hence they are used as medicines and thus glycosylation affects both the hydrophobicity and biological activity of plant natural products [36,37]. However, most are active in glycosylated form. In recent times, glycosides have shown dynamic potential as therapeutic agents in the treatment of different disorders. Some of them includes anticancer [38], antithrombotic and antidiabetic [39,40], protective effect in myocardial injury [41], antioxidant [42], antiviral [43], antidepressant like effect [44,45], antimalarial [46], antifungal [47], antiplatelet [48]. Accordingly, this review provides comprehensive information on the subject of preclinical status of glycosides isolated from various plants as possible candidates for clinical studies to discover better, safer, and more effective treatments against drug-resistant fungi.

4. Preclinical status of anti-fungal glycosides

Several research groups have been involved in the isolation and identification of antifungal activities of glycosides of plant origin (Table 1). In 1988, Hufford et al. isolated pure triterpene acetylated saponins, dioscin **1** with minimum inhibitory concentration (MIC) of 1.56 μg/mL, and pennogenin rhamnosyl chacotrioside **2** (MIC = 6.25 μg/mL) from *Trillium grandiflorum*; these compounds exhibited strong activity against *Candida parapsilosis* and *Candida albican* [49], *Trichosporon. beigelii*, and Malassezia. *furfur* [50]. On the other hand, Carmely et al. isolated a new 4-methylated steroidal glycoside (Eryloside A **3**) from *Erylus lendenfeldi* which displayed significant antifungal activity against *Candida albicans* (MIC 15.6 μg/mL) [51]. A new antifungal glycoside, 3-*O*[α-L-arabinopyranosyl(1–2)][α-L-arabinopyranosyl(1–6)]2-acetoami do-2-deoxy-β-D-gluco-pyranosyl oleanolic acid **4** has been isolated from *Pithecelobium racemosum* by Khan and colleagues; this glycoside displayed remarkable potency against *Trichophyton mentogrophytes*, *Candida albicans* and *Sacharomyces cerevisiae* with MIC values of 6.25, 12.5 and 12.5 μg/mL, respectively [52].

In addition, researchers isolated the new aurantoside D **5**, E, and aurantoside F **6**, which are polyene tetramic acids comprising an *N*-trisaccharide unit, from the ethanol extract of the marine sponge of *Siliquaria spongia japonica*. These researchers found that aurantosides D and E were active against *Aspergillus fumigatus* and *Candida albicans*, whereas F was inactive. Moreover, aurantosides D and E were found to exhibit potent antifungal activity against *Aspergillus fumigatus* and *Candida albicans*, with MIC values of 9.5 and 9.7 μg/mL, respectively, against *Candida albicans*, and MIC values of 11.0 and 13.6 μg/mL, respectively, against *Aspergillus fumigatus* [53]. Furthermore, results from this investigation revealed that aurantosides E and F were significantly active against the spore germination of rice blast fungus *Magnaporthe grisea*. Similarly, the antifungal activity of monodesmosides, isolated from the leaves of *Kalopanax pictum*, was investigated by Lee et al. [54]. These researchers observed that the monodesmosides α-hederin **7**, sapindoside B **8** and sapindoside C **9** exhibit marked antifungal activity against *Microsporum canis*, *Candida immeritis*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, and *Candida albicans* with MIC values of 6.25–25 μg/mL. Furthermore, the aerial parts of *Phlomis samia* led to the isolation of a new phenylethanoid glycoside 1-*O*-3,4-(dihydroxyphenyl)ethyl *β*-D-apiofuranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 3)-4-*O*-caffeoyl-*β*-D-glucopyranoside called samioside **10** which displayed effective antifungal

Table 1
Plant derived glycosides with antifungal activities.

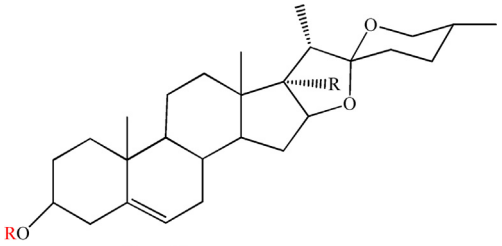
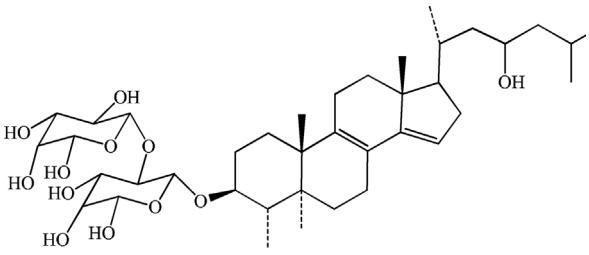
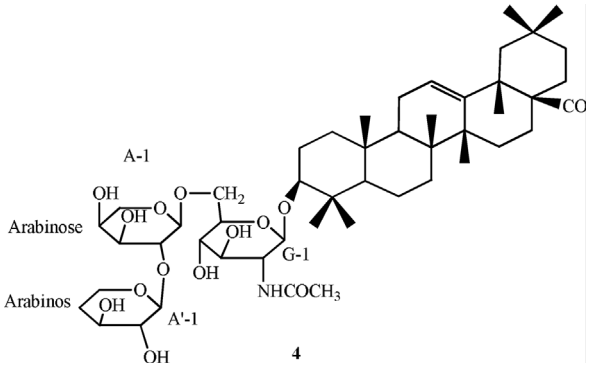
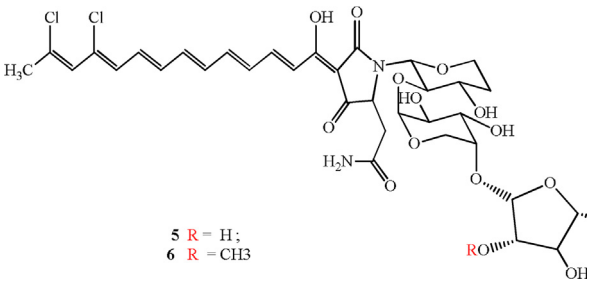
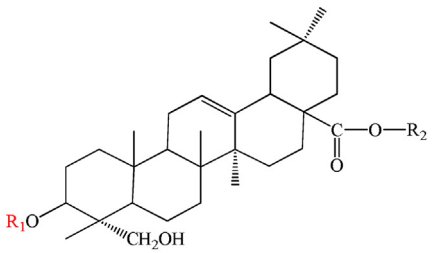
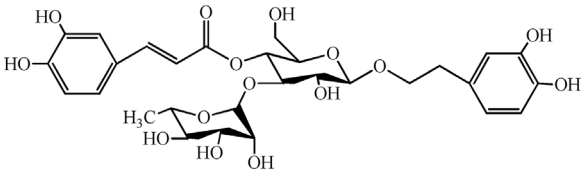
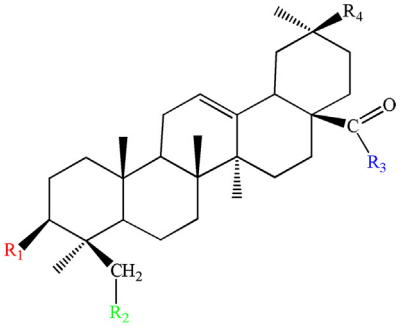
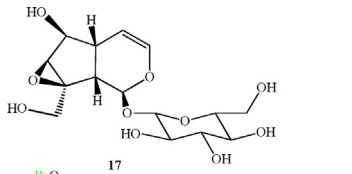
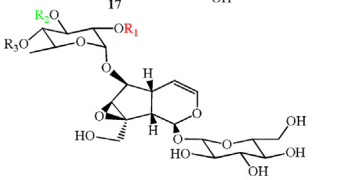
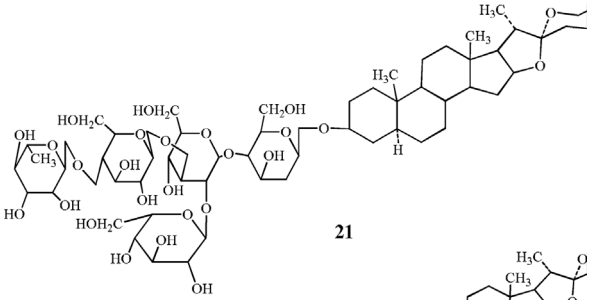
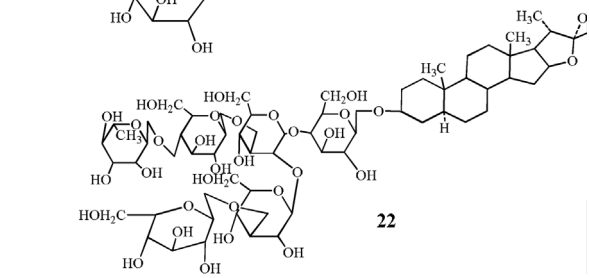
Plant name	Chemical Structure	Reference
Trillium grandiflorum	 R R' **1** H Rham-Glu-Rham **2** OH Rham-Rham-Glu-Rham	[49,50]
Erylus lendenfeldi	 **3**	[51]
Pithecelobium racemosum	 **4**	[52]
Siliquaria spongia	 **5** R = H; **6** R = CH3	[53]
Kalopanax pictum	 R1 R2 **7** α- L-ara2-α-L-rha H **8** α-L-ara2-α-L-rha β-D-glc6-β-D-glc4-α-L-rha **9** α-L-ara2-α-L-rha3-β-D-xyl4-β-D-glc H	[54]

Table 1 (*Continued*)

Plant name	Chemical Structure	Reference
Phlomis samia	 **10**	[55]
Chenopodium quinoa		[56]
Gmelina arborea	 **17** 	[57]
Yucca gloriosa	 **21**  **22**	[58]

	R_1	R_2	R_3	R_4
11	Glc	H	Glc	CH3
12	Ara	OH	Glc	CH3
13	Ara(1→3)	OH	Glc	CH3
14	Ara	OH	OH	COOCH
15	Ara(1→3) Glc	OH	H	COOCH
16	Ara(1→3) Glc	OH	Glc	COOCH

	R_1	R_2	R_3
18	trans-cinnamoyl	H	H
19	H	trans-cinnamoyl	H
20	H	H	trans-cinnamoyl

Table 1 (*Continued*)

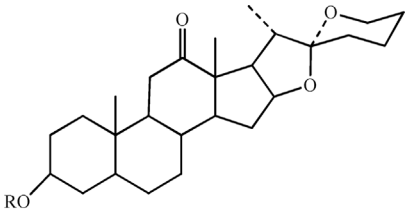
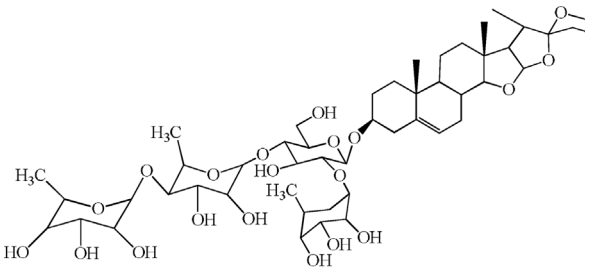
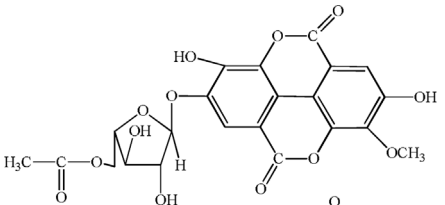
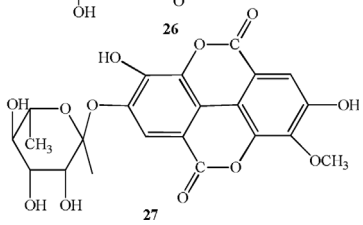
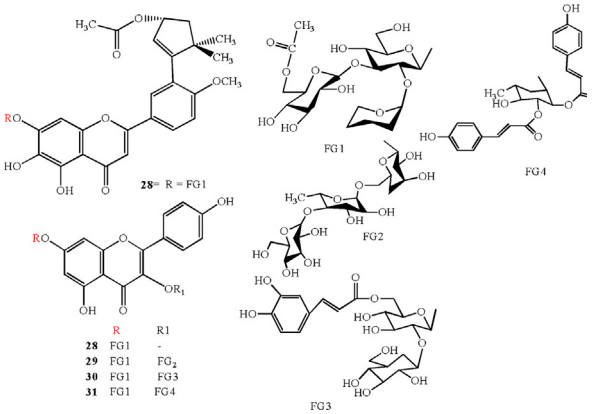
Plant name	Chemical Structure	Reference
Ribulus terrestris	 **23** R=–¦Â–D–gal–¦Â–D–glu–¦Â–D–xyl (2: ¦Â–L–rha; 3: ¦Â–D–xyl) **24** R=–¦Â–D–gal–¦Â–D–glu–¦Â–D–glu (3: ¦Â–D–xyl)	[59]
	 **25**	[60]
Gleditsia sinensis	 **26**  **27**	[61]
Saussurea lappa	 **28**= R = FG1 **28** FG1 - **29** FG1 FG_2 **30** FG1 FG3 **31** FG1 FG4 FG1 FG4 FG2 FG3	[62]

Table 1 (*Continued*)

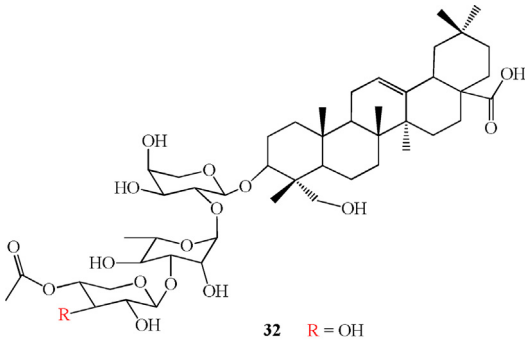
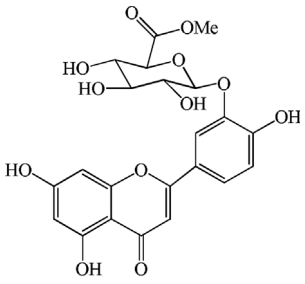
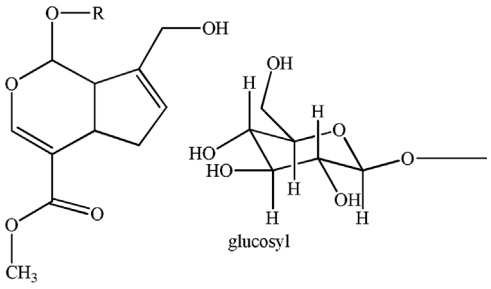
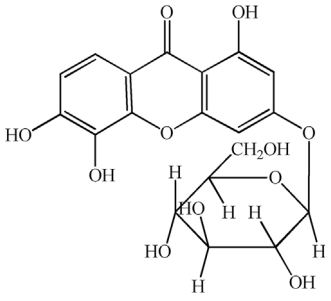
Plant name	Chemical Structure	Reference
Sapindus saponaria	 **32** R = OH **33** R = OAc	[63]
Vitex negundo	 **34**	[64]
Gardenia jasminosides	 **35** = R = glucosyl **36** = R = H	[65]
Peperomia pellucida	 **37**	[66]

Table 1 (*Continued*)

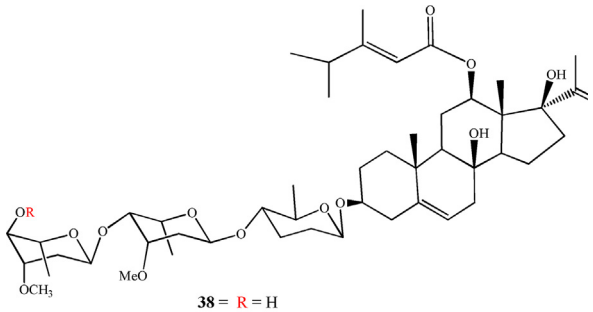
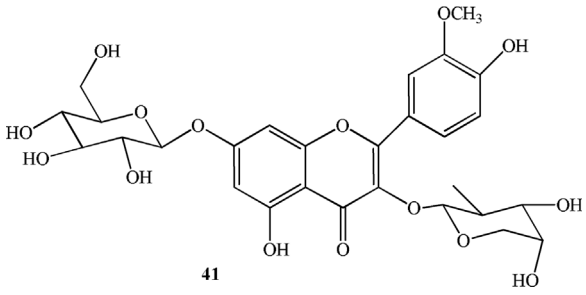
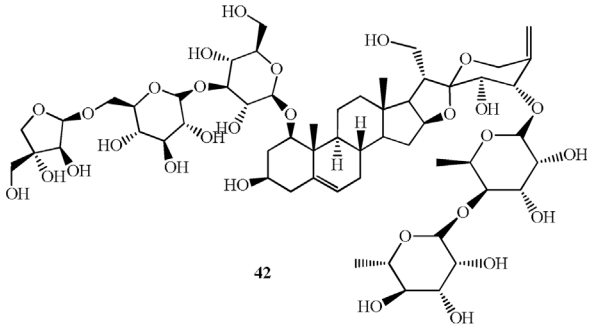
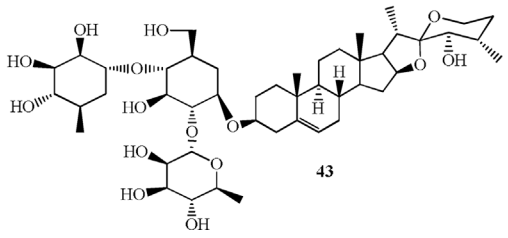
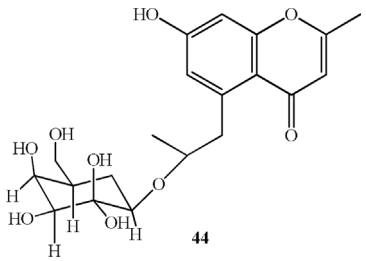
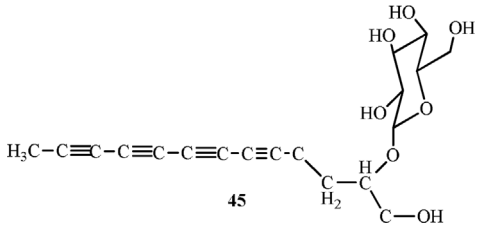
Plant name	Chemical Structure	Reference
Cynanchum wilfordii	 **38** = R = H **39** = R= α-L-glucose-β-D-glucose **40** = R = β-D-glucose	[67]
Callianthemum taipaicum	 **41**	[68]
Trillium govanianum	 **42**  **43**	[69]
Acacia ataxacantha	 **44**	[70]

Table 1 (*Continued*)

Plant name	Chemical Structure	Reference
Bidens pilosa	 **45**	[71]

activity against the pathogenic fungi, *Candida albicans*, *Candida glabrata*, and *Candida tropicalis* [55].

In addition, the following compounds isolated by Woldemichael and Wink from *Chenopodium quinoa*, showed antifungal activity against *Candida albicans*: 3-*O*-*β*-D-glucuronopyranosyl oleanolic acid 28-*O*-*β*-D-glucopyranosyl ester **11** (MIC ≥ 500 μg/mL), 3-*O*-α-L-arabinopyranosyl hederagenin 28-*O*-*β*-D-glucopyranosyl ester **12** (MIC ≥ 500 μg/mL), 3-*O*-*β*-D-glucopyranosyl-(1 → 3)-α-Larabinopyranosyl hederagenin 28-*O*-*β*-D-glucopyranosyl ester **13** (MIC ≥ 500 μg/mL), 3-*O*-α-L-arabinopyranosyl phytolaccagenic acid 28-*O*-*β*-D-glucopyranosyl ester **14** (MIC = > 500 μg/mL), 3-*O*-*β*-D-glucopyranosyl-(1 → 3)-α-L-arabinopyran osyl phytolaccagenic acid 28-*O*-*β*-D-glucopyranosyl ester **15** ((MIC = ≤100 μg/mL), 3-*O*-*β*-D-glucopyranosyl-(1 → 3)-α-L-arabinopyranosyl phytolaccagenic acid **16** (MIC ≥500 μg/mL) [56]. A number of publications pertaining to the isolation and antifungal activity of glycosides have appeared in the literature. Kawamura and Ohara isolated four iridoid glycosides, catalpol **17** 6-*O*-α-L-(2"-*O*-*trans*-cinnamoyl) rhamnopyranosylcatalpol **18**, 6-*O*-α-L-(3"-*O*-*trans*-cinnamoyl)rhamno-pyranosylcatalpol, **19** and 6-*O*-α-L-(4"-*O*-*trans*-cinnamoyl) rhamnopyranosylcatalpol **20** from the methanol extract of the heartwood of *Gmelina arborea* [57]. These researchers have also studied the antifungal activity of isolated compounds against a yeast that causes skin infection called tinea versicolor and found that isolated iridoid glycosides display significant antifungal activity with catalpol being most potent (MIC 0.05 μmol/mL). On the other hand, work by Favel et al. on *Yucca gloriosa* flowers led to the isolation of two spirostanol glycosides, yuccaloeside B **21** and yuccaloeside C **22**. *In vitro* antifungal activity against a panel of human pathogenic fungi, yeasts as well as dermatophytes and filamentous species, revealed that these two isolated glycosides exhibit broad antifungal activity against all studied strains except for *Candida lusitaniae* and *Candida kefyr* with MIC between 0.39 and 6.25 μg/mL [58]. While in phytochemical study of *Ribulus terrestris*, Zhang et al. in 2006, isolated a number of saponins glycosides [59], in which Tigogenin-3-*O*-β-D-xylopyranosyl (1 → 2)-[β-D-xylopyranosyl (1 → 3)]-β-D-glucopyranosyl (1 → 4)-[α-L-rhamnopyranosyl (1 → 2)]-β-D-galactopyranoside **23** and Tigogenin-3-*O*-β-D-glucopyranosyl (1 → 2)-[β-D-xylopyranosyl (1 → 3)]-β-D-glucopyranosyl (1 → 4)-β-D-galactopyranoside **24** showed marked antifungal activity against various test fungi. The marked effects of these compounds in comparison to others isolate, it is assumed that spirostanol skeleton and the number of oligosaccharide residue attached at C-3 of aglycon, are primary for the antifungal. however, carbonyl base at C-12 needs further study to ascertain its relationship with the antifungal action.

Similarly, Sobolewska and colleagues (2006) isolated antifungal steroidal glycosides named as (25R)-spirost-5-en-3β-ol 3-O-α-rhamnopyranosyl-(1 → 4)-α-rhamnopyranosyl-(1 → 4)-[α-rhamnopyranosyl-(1 → 2)]-glucopyranoside **25** [60]. It exhibits antifungal potency with MIC = 200 mg/mL. In addition, Zhou and colleagues isolated two ellagic acid glycosides, a new compound, 3-O-methylellagic acid-4′-(5′′-acetyl)-α-L-arabinofuranoside **26** and a previously known compound, 3-O-methylellagic acid-4′-*O*-α-L-rhamnopyranoside **27** from the ethanol extract of *Gleditsia sinensis* spines. These two compounds played significant antifungal activity against the spore germination of rice blast fungus *Magnaporthe grisea*, with IC_{50} values of 13.56 and 16.14 μg/mL, respectively [61]. In a similar study, Rao et al. isolated four new acylated flavonoid glycosides from the roots of *Saussurea lappa;* 3′-(3R-acetoxy-5,5-dimethylcyclopent-1-ene)-4′-O-methylscutellarein-7-O-(6′′′′-*O*acetyl-β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranoside, **28**, kaempferol-3-*O*-β-D-glucopyransoyl-(1 → 4)-α-L-rhamnopyran osyl-(1 → 6)-β-D-galactopyranoside-7-*O*-(6′′′′-*O*-acetyl-β-D-glucopyranosyl(1 → 3)-[α-L-rhamnopyr anosyl-(1 → 2)]-β-D-glucopyranoside **29**, kaempferol-3-*O*-β-D-glucopyranosyl(1 → 2)-β-D-(6a′-*O*-caffeoyl)-glucopyranoside-7-*O*-(6′′′′-*O*-acetyl-β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyrano syl-(1 → 2)]-β-D-glucopyranoside **30**, and kaempferol-3-*O*-α-L-(2a′,3a′-*E*-di-p-coumaroyl-*p*-coumaroyl)-rhamnoside-7-O-)-rhamnoside-7-*O*-(6′′′′-*O*-acetyl-β-D-glucopyranosyl-(1 → 3)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-gluco pyranoside **31**. These isolated glycosides were bioassay against nine fungi: *Aspergillus niger*, *Aspergillus Ochraceus*, *Aspergillus versicolor*, *Aspergillus flavus*, *Penicillium ochrochloron*, *Penicillium funiculosum*, *Trichoderma viride*, *Cladosporium cladosporioides*, and *Alternaria alternate*. Results revealed greater antifungal activity than the commercial drug miconazole [62].

In an investigation conducted by Tsuzuki et al., two pure triterpene acetylated saponins, 3-*O*-(4-acetyl-β-D-xylopyranosyl)-(1 → 3)-α-L-rhamno pyranosyl-(1 → 2)-α-L-arabinopyranosyl-hederagenin **32** and 3-*O*-(3,4-di-acetyl-β-D-xylopyrano syl)-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl-hederagenin **33** were isolated from *Sapindus saponaria*. These two compounds, in addition to extracts from dried fruits of the plant, were investigated for their antifungal activity against clinical isolates of yeasts *Candida albicans* and non-*Candida albicans* from vaginal secretions of women with vulvovaginal candidiasis. Results from this study showed that isolated compounds exhibit strong activity against *Candida parapsilosis* [63]. Similarly, Sathiamoorthy and co-researchers isolated a new flavone glycoside 4',5,7-trihydroxy-3'-*O*-β-D-glucuronic acid-6"-methyl ester **34** from leaf ethanol extract of *Vitex negundo* with high potency against both *Trichophyton mentagrophytes* and *Cryptococcus neoformans* (MIC = 6.25 μg/mL) [64]. Interestingly, Lelono et al. identified two antifungal compounds, genipin and geniposide from the methanol extract of leaves and stems of *Gardenia jasminosides*. These two compounds displayed remarkable antifungal activity against a wood rotting fungus *Pleurotus ostreatus* [65]. In addition, research

showed that both compounds genipin **35** and geniposide **36** exhibit effective antifungal effect against pathogenic fungi, *Fusarium oxysporum* and *Candida cassiicola*. Structure activity relationship (SAR) studies suggest that the lactone group present in these compounds may be responsible for their antifungal activity because it penetrates fungal cells and reacts with sulphydryl group. In addition, phytochemical analysis led to the isolation of xanthone glycoside, patuloside A **37** from the leaves of *Peperomia pellucida* [66].

Furthermore, two new pregnane glycosides, wilfoside K1GG **38** and wilfoside C1GG **39**, along with four known compounds, wilfoside C1N, wilfoside K1N **40**, cynauricuoside A, and wilfoside C1G were isolated from the methanol extract of the dried roots of *Cynanchum wilfordii* by Yoon et al. [67]. These compounds were investigated for antifungal activity against barley powdery mildew caused by *Blumeria graminis* f. sp. hordei. Results indicated that caudatin glycosides display stronger activity, whereas kidjoranine glycosides exhibit weaker antifungal activity than positive control polyoxin B. In a paper recently published, Wang and his co-workers, isolated a new flavanol glycoside, isorhamnetin-3-*O*-α-L-arabinoside-7-*O*-β-D-glucoside, from *Callianthemum taipaicum*. This glycoside showed antifungal activity against *Rhizoctonia cerealis* (MIC 1.92 mg/mL), *Botrytis cinerrea* (MIC 1.38 mg/mL), and *Thanatephorus cucumeris* (MIC 1.39 mg/mL) [68]. Similarly, Ismail and colleagues identified a new spirostane steroidal saponin, govanoside A, along with known compounds, borassoside E **42**, and pennogenin **43**, from the rhizomes of *Trillium govanianum*. Studies showed that *C. albicans* was highly susceptible to govanoside A (MIC = 5.0 μg/mL) and borassoside E pennogenin (MIC = 2.5 μg/mL) [69]. Most recently, Amoussa et al. (2016) isolated a new glycoside with the name of acthaside **44** from *Acacia ataxacantha* [70]. In the antimicrobial assay, it showed antifungal activity against *Candida albicans* with MIC 25 and MFC 50 μg/mL. Additionally, **44** caused significant free radical scavenging effect which further potentiate its therapeutic potential. Likewise, cytopiloyne **45** a glycoside isolated from *Bidens pilosa* with multiple medicinal uses in traditional system of treatment [71]. When studied for detail antifungal activity with possible mechanism, it showed marked effects were observed.

5. Mechanism(s) of phytoglycosides

Researchers around the world have extensively investigated the underlying mechanisms for antifungal sensitivity of phytoglycosides (Fig. 1).

On their work on the methanol extract of seeds of *Chenopodium quinoa*, Woldemichael and Wink isolated at least 16 saponins. These researchers evaluated the antifungal activity of these compounds against *Candida albicans* and hemolytic activity on erythrocytes. Results revealed that these compounds and derived monodesmosides, bidesmosides and derived monodesmosides display little or no antifungal activity, whereas monodesmosides exhibit higher degree of hemolytic activity. They concluded that monodesmoside saponins, having oleanolic acid and hederagenin as aglycon, are highly hemolytic and exhibit higher antimycotic activity [56]. On the other hand, Favel et al. suggested the antimycotic properties of spirostanol glycosides are attributed to their ability to complex with sterols of fungal membranes, which produce spore-like structures that lead to rupture of the membrane leading to fungal cell death [58]. Similar results were obtained by Lunga and colleagues after they investigated the phytochemical analysis of seeds of *Hyocyamus niger* L. and ascribed the antifungal activity of these compounds to formation of complex with sterols in fungal membranes which causes pore formations in membrane and loss in membrane integrity [72]. Similarly, results from an investigation by Zhang et al. showed that

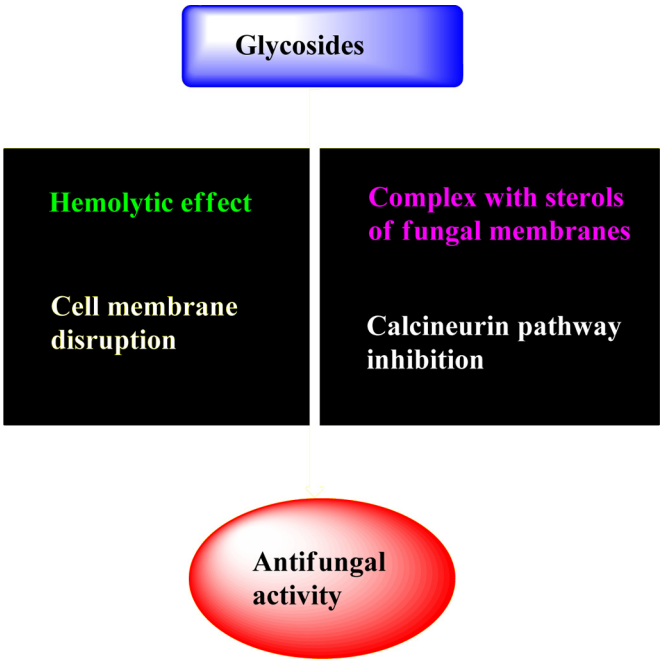


Fig. 1. Proposed antifungal mechanisms of plant glycosides.

the mechanism of antifungal glycosides was damaging of the plasma membrane and leakage of cytoplasmic material which leads to cell death [59]. Similarly, with the aid of flow cytometric analysis, Park et al. evaluated the antifungal activity of styraxjaponoside A and B, antifungal lignan glycosides extracted from the stem bark of *S .japonica*, against a number of human pathogenic fungal strains. They attributed the activity to membrane–disruption mechanisms [73]. Likewise, a recent review by Freiesleben and Jäger suggested the mechanism of action of steryl glycosides is through cell membrane disruption. After complex formation with cholesterol, they attach to lipophilic moiety inside the membrane and hydrophilic moiety outside the cell, and hence suppress the growth of fungi [74].

On the other hand, Shrestha et al. ascribed the antifungal property of glycosides to increasing plasma membrane permeability, that causes leakage of pre-loaded calcein from 50% of small unilamellar vesicles with sterol and glycerophospholipid composition of the plasma membrane of *Sacharomyces cerevisiae* [75]. Lee and colleagues reported that the antifungal activity of magnoloside A against various *Cryptococcus* species, is due to its inhibition of the calcineurin pathway. Calcineurin is a highly specific, Ca^{2+}-dependent serinethreonine phosphatase which has an important role in mediating cell stress responses [76]. Other researchers have also inferred involvement of calcineurin pathway in the growth and pathogenesis of several fungal species, such as *C. albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*, in diseases caused by fungal infections [77]. Based on the various mechanisms described/reported for the phytoglycosides as antifungal agents reveled that their actions mediated through different and multiple targets, therefore, it can be assumed that they may be more resistant to fungal modifications for drug resistance. To know the answer of such questions, further detail studies are required.

6. Effect of sugar moiety on the antifungal activity

Sugar (glycone) part in glycosides are mostly inactive in terms of activity but sometime crucial for the overall effect. For instance, monodesmoside saponins, having oleanolic acid and hederagenin

as aglycon, are highly hemolytic and exhibit higher antimycotic activity. Furthermore, addition of a glucose unit on the C-3 chain, and introduction of an additional carboxy group on ring E dramatically reduce hemolytic activity because hydrophobic interactions with membrane lipids become reduced [56].

SAR studies revealed that the stronger activity of caudatin glycosides is due to the presence of an ikemaoyl group at C-12, whereas kidjoranine glycosides have cinnamoyl group [67]. Additionally, the antimycotic action of the pregnane glycosides was increased by removal of a sugar moiety at C-3. Results also showed that patuloside A (MIC = 18.24 μg/mL) has weak antifungal activities against *Aspergillus flavus* and *Candida albicans*.

Quite recently, Ismail and colleagues reported that pharmacological activity of antifungal compounds was affected by the number of sugar moieties linked with the aglycon portion of steroidal nuclei. For example the antifungal activity of govanoside A having five sugar units is less, as compared to borassoside E with three sugar units. They concluded that a high number of sugar units increases polarity of the glycoside, and hence makes it difficult to cross fungal membranes [69].

7. Utilization of technology

Drug development is greatly facilitated by the recent advancement in technologies and genetic studies [35,78,79]. For instance, studies have shown members of the ALS gene family encoding adhesins play an important role for interactions of *C. albicans* with host tissues [80]. Similarly, the epithelial adhesin (EPA) gene family account for the largest group in *C. glabrata*, comprising at least 23 related genes, most of them located in subtelomeric regions [81,82]. The primary EPA including, Epa1, Epa6 and Epa7, display different binding specificities concerning decoration of host cell ligands containing a terminal galactose residue [83,84]. The computational studies also have provided a strong theoretical foundation for the correlation of biological system with computer based results [85–87] and thus play a significant in overall new drug discovery. The major advantage of such techniques is theoretical modification of results and thus derisible outcome can be achieved.

Additionally, the introduction of different dosage forms have improved therapeutic outcomes and ultimate results [88]. The nanotechnologies are widely used for the rectification of various pharmacokinetic limitations in drug candidates from natural sources [10,89]. In recent years, nanotechnology has driven efforts toward this therapeutic area, proposing efficient colloidal (nanosized) delivery systems (NDDS) that have attained in some cases a market significance and clinical relevance. NDDS can control the release of loaded drugs or target their distribution within the body, focusing selectively their activity in the infected cells, thus reducing side effects. Loading of antifungals including food materials, in nanocarriers through physical encapsulation, adsorption, or chemical conjugation, makes it possible to overwhelm their poor solubility and improve pharmacokinetics and therapeutic index, compared to the neat drugs [90–92].

8. Conclusions and future prospect

This review covers glycosides derived from medicinal plants, which are traditionally used for the treatment of fungal diseases. Results showed that isolated plant glycosides exhibited profound sensitivity against various fungi and the effects were not limited to one particular plant family or class of glycosides. These outstanding preclinical results deserve the utmost attention of pharma-industry for further detail studies to move towards some conclusions and identification of clinically useful agents. In addition, mechanistic studies revealed that these natural glycosides exert their effects through multiple mechanisms, unlike synthetic standard antifungal agents such as amphotericin B, which acts by binding to the sterol component of a cell membrane, leading to alterations in cell permeability and cell death, or fluconazole which is a highly selective inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-α-demethylase for fungistatic effect, and thus having numerous side effects.

While considering the different sites of antifungal action/mechanisms, it could be assumed that these glycosides might be less proven to resistance and have better tolerability to cope with the current emergence of resistant to various synthetic agents. Moreover, the latest development in the drug discovery techniques for natural product further encourages researchers to work on the isolation and characterization of phytopharmaceuticals that could lead to some outstanding hits. In this connection, these preliminary effects need further detailed studies including mechanism exploration, safety profile and clinical trials for the discovery of clinically useful drugs.

Disclosure

Authors of this article have no conflict of interest.

References

[1] M. McCarthy, A. Rosengart, A.N. Schuetz, D.P. Kontoyiannis, T.J. Walsh, Mold infections of the central nervous system, N. Engl. J. Med. 371 (2014) 150–160.

[2] F. De Bernardis, M. Amacker, S. Arancia, S. Sandini, C. Gremion, R. Zurbriggen, C. Moser, A. Cassone, A virosomal vaccine against candidal vaginitis: immunogenicity: efficacy and safety profile in animal models, Vaccine 30 (2012) 4490–4498.

[3] T. Nakama, S. Yamashita, T. Hirahara, S. Okamoto, S. Honda, M. Watanabe, E. Kimura, M. Uchino, S. Yano, J.-i. Kuratsu, Y. Ando, Usefulness of intraventricular infusion of antifungal drugs through Ommaya reservoirs for cryptococcal meningitis treatment, J. Neurolog. Sci. 358 (2015) 259–262.

[4] D.V.C. Mendonça, L.M.R. Lage, D.P. Lage, M.A. Chávez-Fumagalli, F. Ludolf, B.M. Roatt, D. Menezes-Souza, A.A.G. Faraco, R.O. Castilho, C.A.P. Tavares, J.M. Barichello, M.C. Duarte, E.A.F. Coelho, Poloxamer 407 (Pluronic® F127)-based polymeric micelles for amphotericin B: In vitro biological activity, toxicity and in vivo therapeutic efficacy against murine tegumentary leishmaniasis, Exper. Parasitol. 169 (2016) 34–42.

[5] D.S. McManus, Chapter 25 – antifungal drugs, in: D.R. Sidhartha (Ed.), Side Effects of Drugs Annual, Elsevier, 2016, pp. 243–253.

[6] E.W. Bachtiar, S. Dewiyani, S.M. Surono Akbar, B.M. Bachtiar, Inhibition of *Candida albicans* biofilm development by unencapsulated Enterococcus faecalis cps2, J. Dental Sci. 11 (2016) 323–330.

[7] J.D. Sobel, J.F. Fisher, C.A. Kauffman, C.A. Newman, Candida urinary tract infections—epidemiology, Clin. Inf. Dis. 52 (2011) S433–S436.

[8] B. Pilmis, A. Puel, O. Lortholary, F. Lanternier, New clinical phenotypes of fungal infections in special hosts, Clin. Microbiol. Inf. 22 (2016) 681–687.

[9] A. Zida, S. Bamba, A. Yacouba, R. Ouedraogo-Traore, R.T. Guiguemdé, Anti-Candida albicans natural products: sources of new antifungal drugs: a review, Journal de Mycologie Médicale/J. Med. Mycol. 27 (2017) 1–19.

[10] G.M. Soliman, Nanoparticles as safe and effective delivery systems of antifungal agents: achievements and challenges, Inter. J. Pharm. 523 (2017) 15–32.

[11] F. Peláez, A. Cabello, G. Platas, M.T. Díez, A.G. del Val, A. Basilio, I. Martán, F. Vicente, G.F. Bills, R.A. Giacobbe, R.E. Schwartz, J.C. Onishi, M.S. Meinz, G.K. Abruzzo, A.M. Flattery, L. Kong, M.B. Kurtz, The discovery of enfumafungin: a novel antifungal compound produced by an endophytic hormonema species biological activity and taxonomy of the producing organisms, Syst. Appl. Microbiol. 23 (2000) 333–343.

[12] C. Jiménez-Ortigosa, P. Paderu, M.R. Motyl, D.S. Perlin, Enfumafungin derivative MK-3118 shows increased in vitro potency against clinical echinocandin-resistant *Candida* species and *Aspergillus* species isolates, Antimicrob. Agents Chemother. 58 (2014) 1248–1251.

[13] H. Khan, M. Saeed, A. Rauf, M.A. Khan, N. Muhammad, Antimicrobial and inhibition on heat-induced protein denaturation of constituents isolated from *Polygonatum verticillatum* rhizomes, Nat. Prod. Res. 29 (2015) 2160–2163.

[14] A.K. Murad, I. Humaira, K. Haroon, S. Mohammmad, K. Ikhtair, Antimicrobial activities of the whole plant of *Cestrum nocturnum* against pathogenic microorganisms, Afr. J. Microbiol. Res. 5 (2011) 612–616.

[15] S. Amin, H. Khan, Revival of natural products: utilization of modern technologies, Curr. Bioactive Comp. 12 (2016) 103–106.

[16] H. Khan, Brilliant future of phytomedicines in the light of latest technological developments, J. Phytopharmacol. 4 (2015) 58–60.

[17] H. Khan, Medicinal plants in light of history recognized therapeutic modality, J. Evid. Based Compl. Altern. Med. 19 (2014) 216–219.

[18] A. Pervaiz, R. Khan, F. Anwar, M.A. Kamal, G. Mushtaq, H. Khan, Alkaloids: an emerging antibacterial modality against Methicillin Resistant *Staphylococcus aureus*, Curr. Pharm. Des. 22 (2016) 4420–4429.

[19] H. Khan, M.A. Khan, A. Dullah, Antibacterial antioxidant and cytotoxic studies of total saponin, alkaloid and sterols contents of decoction of Joshanda: identification of components identification through thin layer chromatography, Toxicol. Ind. Health 31 (2015) 202–208.

[20] H. Khan, M. Saeed, N. Muhammad, S. Perviz, Phytochemical analysis antibacterial, and antifungal assessment of aerial parts of *Polygonatum verticillatum*, Toxicol. Ind. Health 32 (2016) 841–847.

[21] S. Khattak, H. Khan, Anti-cancer potential of phyto-alkaloids: a prospective review, Curr. Can. Ther. Rev. 12 (2016) 66–75.

[22] S. Rehman, H. Khan, Advances in antioxidant potential of natural alkaloids, Curr. Bioactive Comp. (2016) Accepted.

[23] E.G. Poage, J.R. Rodrick, A. Wanchai, B.R. Stewart, J.N. Cormier, J.M. Armer, Exploring the usefulness of botanicals as an adjunctive treatment for lymphedema: a systematic sea, Rev. PM&R 7 (2015) 296–310.

[24] P. Vandeputte, S. Ferrari, A.T. Coste, Antifungal resistance and new strategies to control fungal infections, Int. J. Microbiol. 2011 (2012), doi:http://dx.doi.org/10.1155/2012/713687.

[25] M.A. Pfaller, Antifungal drug resistance: mechanisms epidemiology, and consequences for treatment, Am. J. Med. 125 (2012) S3–S13.

[26] D.P. Kontoyiannis, R.E. Lewis, Antifungal drug resistance of pathogenic fungi, Lancet 359 (2002) 1135–1144.

[27] A.D. Ribas e Ribas, P. Spolti, E.M. Del Ponte, K.Z. Donato, H. Schrekker, A.M. Fuentefria, Is the emergence of fungal resistance to medical triazoles related to their use in the agroecosystems? A mini review, Braz. J. Microbiol. 47 (2016) 793–799.

[28] J.L. Xie, E.J. Polvi, T. Shekhar-Guturja, L.E. Cowen, Elucidating drug resistance in human fungal pathogens, Fut. Microbiol. 9 (2014) 523–542.

[29] R. Arreche, N. Bellotti, C. Deyá, P. Vázquez, Assessment of waterborne coatings formulated with sol-gel/Ag related to fungal growth resistance, Prog. Org. Coat. 108 (2017) 36–43.

[30] A. Busca, A.M. Tortorano, L. Pagano, Reviewing the importance and evolution of fungal infections and potential antifungal resistance in haematological patients, J. Glob. Antimicrob. Resis. 3 (2015) 237–241.

[31] L.A. Hadwiger, Nonhost resistance: self-inflicted DNA damage by fungal DNase accumulation is a major factor in terminating fungal growth in the pea-Fusarium solani f sp. phaseoli interaction, Physiol. Mol. Plant Pathol. 92 (2015) 79–87.

[32] M. Ezoddin, K. Abdi, Monitoring of antifungal drugs in biological samples using ultrasonic-assisted supramolecular dispersive liquid–liquid microextraction based on solidification of a floating organic droplet, J. Chromatogr. B 1027 (2016) 74–80.

[33] M.A. Kalam, S. Alshehri, A. Alshamsan, A. Haque, F. Shakeel, Solid liquid equilibrium of an antifungal drug itraconazole in different neat solvents: determination and correlation, J. Mol. Liquids 234 (2017) 81–87.

[34] Y.-W. Lai, L.T. Campbell, M.R. Wilkins, C.N.I. Pang, S. Chen, D.A. Carter, Synergy and antagonism between iron chelators and antifungal drugs in Cryptococcus, Inter. J. Antimicrob. Agents 48 (2016) 388–394.

[35] A.F. Maheux, A. Sellam, Y. Piché, M. Boissinot, R. Pelletier, D.K. Boudreau, F.J. Picard, H. Trépanier, M.-J. Boily, M. Ouellette, P.H. Roy, M.G. Bergeron, Use of phylogenetical analysis to predict susceptibility of pathogenic Candida spp. to antifungal drugs, J. Microbiol. Methods 131 (2016) 51–60.

[36] G. Serafini, M. Pompili, M. Innamorati, G. Giordano, R. Tatarelli, D. Lester, P. Girardi, Y. Dwivedi, Glycosides: depression and suicidal behaviour: the role of glycoside-linked proteins, Molecules 16 (2011) 2688–2713.

[37] R.V. Stick, S.J. Williams, Chapter 7 – enzymatic cleavage of glycosides: mechanism, inhibition and synthetic applications, Carbohydrates: The Essential Molecules of Life, Second Edition), Elsevier, Oxford, 2009, pp. 253–284.

[38] K. Anand, Maoquan Zhou, Neelam Azad, Hosam Elbaz, Leo Wang, K. Derek, Yon Rojanasakul, A. George, M. Joseph, A direct comparison of the anticancer activities of digitoxin MeON-neoglycosides and O-glycosides, Med. Chem. Lett. 1 (2010) 326–330.

[39] P.-H. Nguyen, V.V. Dung, B.T. Zhao, Y.H. Kim, B.S. Min, M.H. Woo, Antithrombotic and antidiabetic flavonoid glycosides from the grains of *Sorghum bicolor* (L.) Moench var. hwanggeumchal, Arch. Pharm. Res. 37 (2014) 1394–1402.

[40] Z.-X. Liu, C.-T. Liu, Q.-B. Liu, J. Ren, L.-Z. Li, X.-X. Huang, Z.-Z. Wang, S.-J. Song, Iridoid glycosides from the flower buds of *Lonicera japonica* and their nitric oxide production and α-glucosidase inhibitory activities, J. Fun. Foods 18 (Part A) (2015) 512–519.

[41] Y. Fei, J. Zhao, Y. Liu, X. Li, Q. Xu, T. Wang, I.A. Khan, S. Yang, New monoterpene glycosides from sunflower seeds and their protective effects against H2O2-induced myocardial cell injury, Food Chem. 187 (2015) 385–390.

[42] X. Niu, D. Xu, J. Luo, L. Kong, Main iridoid glycosides and HPLC/DAD-Q-TOF-MS/MS profile of glycosides from the antioxidant extract of Eucommia ulmoides Oliver seeds, Ind. Crops Prod. 79 (2016) 160–169.

[43] X.-p. Hu, M.-m. Shao, X. Song, X.-l. Wu, L. Qi, K. Zheng, L. Fan, C.-h. Liao, C.-y. Li, J. He, Y.-j. Hu, H.-q. Wu, S.-h. Li, J. Zhang, F.-x. Zhang, Z.-d. He, Anti-influenza virus effects of crude phenylethanoid glycosides isolated from ligustrum purpurascens via inducing endogenous interferon-γ, J. Ethnopharmacol. 179 (2016) 128–136.

[44] X. Li, Y. Luo, G.-P. Li, Q.-X. Yang, Pregnane glycosides from the antidepressant active fraction of cultivated *Cynanchum otophyllum*, Fitoterapia 110 (2016) 96–102.

[45] Z.-l. Zhou, W.-Q. Yin, Y.-M. Yang, C.-H. He, X.-N. Li, C.-P. Zhou, H. Guo, New iridoid glycosides with antidepressant activity isolated from *Cyperus rotundus*, Chem. Pharm. Bull. 64 (2016) 73–77.

[46] Y. Liu, N. Murakami, H. Ji, P. Abreu, S. Zhang, Antimalarial flavonol glycosides from *Euphorbia hirta*, Pharm. Biol. 45 (2007) 278–281.

[47] Z. Wang, H. Zhang, W. Yuan, W. Gong, H. Tang, B. Liu, K. Krohn, L. Li, Y. Yi, W. Zhang, Antifungal nortriterpene and triterpene glycosides from the sea cucumber Apostichopus japonicus Selenka, Food Chem. 132 (2012) 295–300.

[48] P. Wang, Q. Wang, C. Luo, C. Tan, X. Yuan, Iridoid glycosides extracted from Zhizi (Fructus Gardeniae) decrease collagen-induced platelet aggregation and reduce carotid artery thrombosis in an in vivo rat model, J. Tradit. Chin. Med. 33 (2013) 531–534.

[49] C.D. Hufford, S. Liu, A.M. Clark, Antifungal activity of Trillium grandiflorum constituents, J. Nat. Prod. 51 (1988) 94–98.

[50] J. Cho, H. Choi, J. Lee, M.-S. Kim, H.-Y. Sohn, D.G. Lee, The antifungal activity and membrane-disruptive action of dioscin extracted from Dioscorea nipponica, Biochim. et Biophys. Acta (BBA) Biomembr. 1828 (2013) 1153–1158.

[51] S. Carmely, M. Roll, Y. Loya, Y. Kashman, The structure of eryloside A: a new antitumor and antifungal 4-methylated steroidal glycoside from the sponge Erylus lendenfeldi, J. Nat. Prod. 52 (1989) 167–170.

[52] I.A. Khan, A.M. Clark, J.D. McChesney, Antifungal activity of a new triterpenoid glycoside from Pithecellobium racemosum (M), Pharm. Res. 14 (1997) 358–361.

[53] N.U. Sata, S. Matsunaga, N. Fusetani, R.W. van Soest, Aurantosides D, E, and F: new antifungal tetramic acid glycosides from the marine sponge Siliquariaspongia j aponica 1, J. Nat. Prod. 62 (1999) 969–971.

[54] M.-W. Lee, S.U. Kim, D.-R. Hahn, Antifungal activity of modified hederagenin glycosides from the leaves of *Kalopanax pictum* var chinense, Biol. Pharm. Bull. 24 (2001) 718–719.

[55] I. Kyriakopoulou, P. Magiatis, A.-L. Skaltsounis, N. Aligiannis, C. Harvala, Samioside, a new phenylethanoid glycoside with free-radical scavenging and antimicrobial activities from Phlomis samia, J. Nat. Prod. 64 (2001) 1095–1097.

[56] G.M. Woldemichael, M. Wink, Identification and biological activities of triterpenoid saponins from Chenopodium quinoa, J. Agric. Food Chem. 49 (2001) 2327–2332.

[57] F. Kawamura, S. Ohara, Antifungal activity of iridoid glycosides from the heartwood of Gmelina arborea, Holzforschung 59 (2005) 153–155.

[58] A. Favel, E. Kemertelidze, M. Benidze, K. Fallague, P. Regli, Antifungal activity of steroidal glycosides from Yucca gloriosa L, Phytother. Res. 19 (2005) 158–161.

[59] J.-D. Zhang, Z. Xu, Y.-B. Cao, H.-S. Chen, L. Yan, M.-M. An, P.-H. Gao, Y. Wang, X.-M. Jia, Y.-Y. Jiang, Antifungal activities and action mechanisms of compounds from *Tribulus terrestris* L, J. Ethnopharmacol. 103 (2006) 76–84.

[60] D. Sobolewska, Z. Janeczko, W. Kisiel, I. Podolak, A. Galanty, D. Trojanowska, Steroidal glycosides from the underground parts of Allium ursinum L. and their cytostatic and antimicrobial activity, Acta Poloniae Pharmaceutica: Drug Res. 63 (2006) 219–223.

[61] L. Zhou, D. Li, W. Jiang, Z. Qin, S. Zhao, M. Qiu, J. Wu, Two ellagic acid glycosides from Gleditsia sinensis Lam with antifungal activity on Magnaporthe grisea, Nat. Prod. Res. 21 (2007) 303–309.

[62] K.S. Rao, G.V. Babu, Y.V. Ramnareddy, Acylated flavone glycosides from the roots of Saussurea lappa and their antifungal activity, Molecules 12 (2007) 328–344.

[63] J.K. Tsuzuki, T.I. Svidzinski, C.S. Shinobu, L.F. Silva, E. Rodrigues-Filho, D.A. Cortez, I.C. Ferreira, Antifungal activity of the extracts and saponins from Sapindus saponaria L, An. Acad. Bras. Cienc. 79 (2007) 577–583.

[64] B. Sathiamoorthy, P. Gupta, M. Kumar, A.K. Chaturvedi, P. Shukla, R. Maurya, New antifungal flavonoid glycoside from Vitex negundo, Bioorg. Med. Chem. Lett. 17 (2007) 239–242.

[65] R. Lelono, S. Tachibana, K. Itoh, Isolation of antifungal compounds from Gardenia jasminoides, Pak. J. Biol. Sci. PJBS 12 (2009) 949–956.

[66] A. Khan, M. Rahman, M.S. Islam, Isolation and bioactivity of a xanthone glycoside from Peperomia pellucida, Life Sci. Med. Res (2010) 2010.

[67] M.-Y. Yoon, N.H. Choi, B.S. Min, G.J. Choi, Y.H. Choi, K.S. Jang, S.-S. Han, B. Cha, J.-C. Kim, Potent in vivo antifungal activity against powdery mildews of pregnane glycosides from the roots of *Cynanchum wilfordii*, J. Agric. Food Chem. 59 (2011) 12210–12216.

[68] D.-M. Wang, W.-J. Pu, Y.-H. Wang, Y.-J. Zhang, S.-S. Wang, A new isorhamnetin glycoside and other phenolic compounds from Callianthemum taipaicum, Molecules 17 (2012) 4595–4603.

[69] M. Ismail, M.R. Shah, A. Adhikari, I. Anis, M.S. Ahmad, M. Khurram, Govanoside A: a new steroidal saponin from rhizomes of Trillium govanianum, Steroids 104 (2015) 270–275.

[70] A.M.O. Amoussa, M. Bourjot, L. Lagnika, C. Vonthron-Sénécheau, A. Sanni, Acthaside: a new chromone derivative from Acacia ataxacantha and its biological activities, BMC Compl. Altern. Med. 16 (2016) 506.

[71] C.-Y. Chung, W.-C. Yang, C.-L. Liang, H.-Y. Liu, S.-K. Lai, C.L.-T. Chang, Cytopiloyne a polyacetylenic glucoside from *Bidens pilosa*, acts as a novel anticandidal agent via regulation of macrophages, J. Ethnopharmacol. 184 (2016) 72–80.

[72] I. Lunga, P. Chintea, S. Shvets, A. Favelb, C. Pizzac, Steroidal glycosides from the seeds of Hyoscyamus niger L and their antifungal activity, Carbon 1 (2007) 3.

[73] C. Park, J.-Y. Cho, B.-M. Hwang, I.-S. Hwang, M.-R. Kim, E.-R. Woo, D.-G. Lee, Styraxjaponoside a and B: antifungal lignan glycosides isolated from Styrax japonica S. et Z, Biomol. Therap. 18 (2010) 420–425.
[74] S.H. Freiesleben, A.K. Jäger, Correlation between plant secondary metabolites and their antifungal mechanisms? A review, Med. Aromatic Plants (2014) 2014.
[75] S. Shrestha, M. Grilley, M.Y. Fosso, C.-W.T. Chang, J.Y. Takemoto, Membrane lipid-modulated mechanism of action and non-cytotoxicity of novel fungicide aminoglycoside FG08, PLoS One 8 (2013) e73843.
[76] W.J. Lee, J.S. Moon, S.I. Kim, Y.-S. Bahn, H. Lee, T.H. Kang, H.M. Shin, S.U. Kim, A phenylpropanoid glycoside as a calcineurin inhibitor isolated from Magnolia obovata Thunb, J. Microbiol. Biotechnol. 25 (2015) 1429–1432.
[77] W.J. Steinbach, J.L. Reedy, R.A. Cramer, J.R. Perfect, J. Heitman, Harnessing calcineurin as a novel anti-infective agent against invasive fungal infections, Nat. Rev. Microbiol. 5 (2007) 418–430.
[78] J. Kim, Y.-J. Cho, E. Do, J. Choi, G. Hu, B. Cadieux, J. Chun, Y. Lee, J.W. Kronstad, W. H. Jung, A defect in iron uptake enhances the susceptibility of Cryptococcus neoformans to azole antifungal drugs, Fungal Gen. Biol. 49 (2012) 955–966.
[79] F.-f. Liu, L. Pu, Q.-q. Zheng, Y.-w. Zhang, R.-s. Gao, X.-s. Xu, S.-z. Zhang, L. Lu, Calcium signaling mediates antifungal activity of triazole drugs in the Aspergilli, Fungal Gen. Biol. 81 (2015) 182–190.
[80] Michael Tscherner, T. Schwarzmüller, K. Kuchler, Pathogenesis and antifungal drug resistance of the human fungal pathogen *Candida glabrata*, Pharmaceuticals 4 (2011) 169–186.
[81] A. De Las Penas, S. Pan, I. Castano, J. Alder, R. Cregg, B. Cormack, Virulence-related surface glycoproteins in the yeast pathogen Candida glabrataare encoded in subtelomeric clusters and subject to RAP1- and SIR-dependent transcriptional silencing, Genes Dev. 17 (2003) 2245–2258.
[82] S. Campoy, J.L. Adrio, Antifungals, Biochem. Pharmacol. 133 (2017) 86–96.
[83] M. Zupancic, M. Frieman, D. Smith, R. Alvarez, R. Cummings, B. Cormack, Glycan microarray analysis of *Candida glabrata* adhesin ligand specificity, Mol. Microbiol. 68 (2008) 547–559.
[84] E. Delarze, D. Sanglard, Defining the frontiers between antifungal resistance: tolerance and the concept of persistence, Drug Resis. Updates 23 (2015) 12–19.
[85] F. Bohlooli, S. Sepehri, N. Razzaghi-Asl, Response surface methodology in drug design: a case study on docking analysis of a potent antifungal fluconazole, Comput. Biol. Chem. 67 (2017) 158–173.
[86] İ.S. Doğan, S. Saraç, S. Sari, D. Kart, Ş. Eşsiz Gökhan, İ. Vural, S. Dalkara, New azole derivatives showing antimicrobial effects and their mechanism of antifungal activity by molecular modeling studies, Eur. J. Med. Chem. 130 (2017) 124–138.
[87] S.K.J. Shaikh, R.R. Kamble, S.M. Somagond, H.C. Devarajegowda, S.R. Dixit, S.D. Joshi, Tetrazolylmethyl quinolines: design docking studies, synthesis, anticancer and antifungal analyses, Eur. J. Med. Chem. 128 (2017) 258–273.
[88] Q. Yu, C. Jia, Y. Dong, B. Zhang, C. Xiao, Y. Chen, Y. Wang, X. Li, L. Wang, B. Zhang, M. Li, Candida albicans autophagy: no longer a bystander: its role in tolerance to ER stress-related antifungal drugs, Fungal Gen. Biol. 81 (2015) 238–249.
[89] F.J. Azeredo, S.E. Hass, P. Sansone, H. Derendorf, T.D. Costa, B.V. De Araujo, Does the anesthetic urethane influence the pharmacokinetics of antifungal drugs? a population pharmacokinetic investigation in rats, J. Pharm. Sci. 104 (2015) 3314–3318.
[90] P.I. Dolez, Chapter 1.1 – nanomaterials definitions, classifications, and applications, Nanoengineering, Elsevier, Amsterdam, 2015, pp. 3–40.
[91] E. Fortunati, D. Puglia, I. Armentano, A. Valdés, M. Ramos, N. Juárez, M.C. Garrigós, J.M. Kenny, 8 – Multifunctional Antimicrobial Nanocomposites for Food Packaging Applications A2 – Grumezescu, Alexandru Mihai, Food Preservation, Academic Press, 2017, pp. 265–303.
[92] P.M. Furneri, G.P. Petronio, V. Fuochi, S. Cupri, R. Pignatello, Chapter 23 – Nanosized devices as antibiotics and antifungals delivery: past, news, and outlook A2 – Andronescu, Ecaterina, in: A.M. Grumezescu (Ed.), Nanostructures for Drug Delivery, Elsevier, 2017, pp. 697–748.