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## Review

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



Haroon Khan<sup>a,\*</sup>, Ziyad Khan<sup>a,1</sup>, Surriya Amin<sup>b,1</sup>, Yahia Nasser Mabkhot<sup>c,1</sup>,  
 Mohammad S. Mubarak<sup>d,\*</sup>, Taibi Ben Hadda<sup>e,1</sup>, Francesco Maione<sup>f,1</sup>

<sup>a</sup> Department of Pharmacy, Abdul Wali Khan University Mardan, 23200, Pakistan

<sup>b</sup> Department of Botany, Islamia College University Peshawar, Pakistan

<sup>c</sup> Department of Chemistry, College of Science, King Saud University, P. O. Box 2455, Riyadh-11451, Saudi Arabia

<sup>d</sup> Department of Chemistry, The University of Jordan, Amman 11942, Jordan

<sup>e</sup> LCM Laboratory, University of Mohammed 1st, Faculty of Sciences, Oujda 60000, Morocco

<sup>f</sup> Department of Pharmacy, University of Naples Federico II, Via Domenico Montesano 49, 80031, Naples, Italy

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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 phyto-glycosides, mediated through multiple mechanisms. Further detailed studies are needed to explain the clinical applications and limitations of these glycosides.

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## 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

\* Corresponding authors.

E-mail addresses: [hkdr2006@gmail.com](mailto:hkdr2006@gmail.com) (H. Khan), [mmubarak@ju.edu.jo](mailto:mmubarak@ju.edu.jo) (M.S. Mubarak).

<sup>1</sup> Authors contributed equally to this work.

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 albicans* [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 ramosum* by Khan and colleagues; this glycoside displayed remarkable potency against *Trichophyton mentagrophytes*, *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** (Continued)

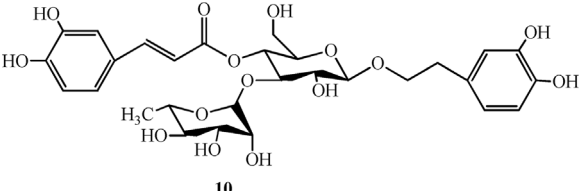
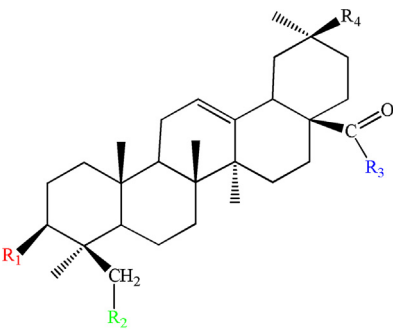
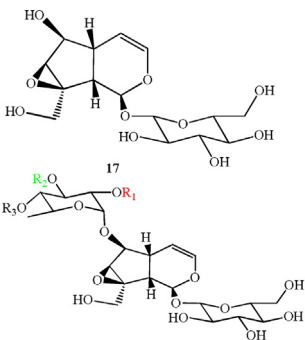
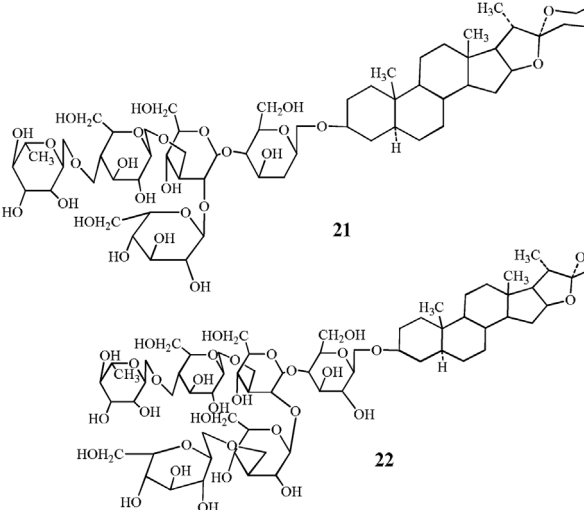
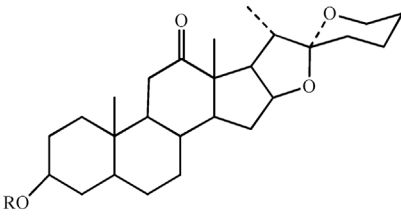
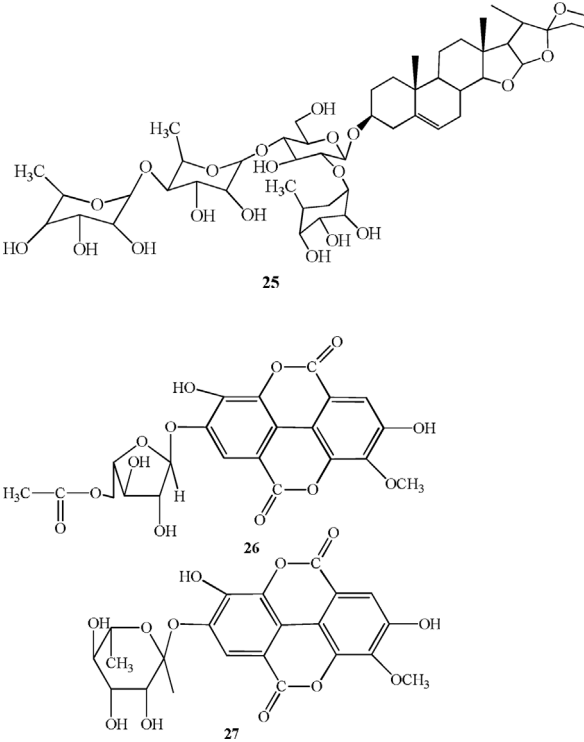
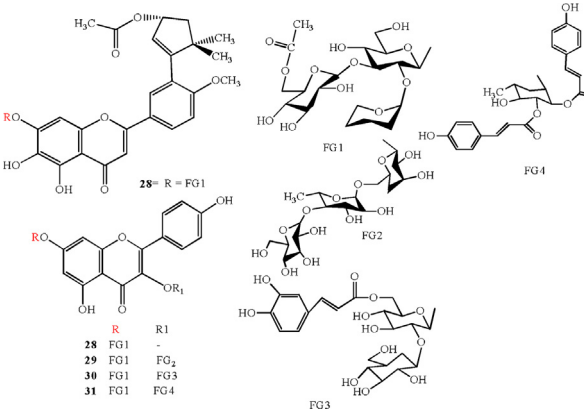
Plant name	Chemical Structure	Reference																																			
<i>Phlomis samia</i>	 <p style="text-align: center;"><b>10</b></p>	[55]																																			
<i>Chenopodium quinoa</i>	 <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>R<sub>1</sub></th> <th>R<sub>2</sub></th> <th>R<sub>3</sub></th> <th>R<sub>4</sub></th> </tr> </thead> <tbody> <tr> <td><b>11</b></td> <td>Glc</td> <td>H</td> <td>Glc</td> <td>CH<sub>3</sub></td> </tr> <tr> <td><b>12</b></td> <td>Ara</td> <td>OH</td> <td>Glc</td> <td>CH<sub>3</sub></td> </tr> <tr> <td><b>13</b></td> <td>Ara(1→3)</td> <td>OH</td> <td>Glc</td> <td>CH<sub>3</sub></td> </tr> <tr> <td><b>14</b></td> <td>Ara</td> <td>OH</td> <td>OH</td> <td>COOCH</td> </tr> <tr> <td><b>15</b></td> <td>Ara(1→3) Glc</td> <td>OH</td> <td>H</td> <td>COOCH</td> </tr> <tr> <td><b>16</b></td> <td>Ara(1→3) Glc</td> <td>OH</td> <td>Glc</td> <td>COOCH</td> </tr> </tbody> </table>		R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	<b>11</b>	Glc	H	Glc	CH <sub>3</sub>	<b>12</b>	Ara	OH	Glc	CH <sub>3</sub>	<b>13</b>	Ara(1→3)	OH	Glc	CH <sub>3</sub>	<b>14</b>	Ara	OH	OH	COOCH	<b>15</b>	Ara(1→3) Glc	OH	H	COOCH	<b>16</b>	Ara(1→3) Glc	OH	Glc	COOCH	[56]
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<i>Yucca gloriosa</i>	 <p style="text-align: center;"><b>21</b></p> <p style="text-align: center;"><b>22</b></p>	[58]																																			

Table 1 (Continued)

Plant name	Chemical Structure	Reference										
<i>Ribulus terrestris</i>	 <p data-bbox="576 449 911 576"> <b>23</b> R = -<math>\beta</math>-D-gal<math>\xrightarrow{2}</math>-<math>\beta</math>-D-glu<math>\xrightarrow{3}</math>-<math>\beta</math>-D-xyf  <math>\beta</math>-L-rha <math>\beta</math>-D-xyf  <b>24</b> R = -<math>\beta</math>-D-gal<math>\xrightarrow{2}</math>-<math>\beta</math>-D-glu<math>\xrightarrow{3}</math>-<math>\beta</math>-D-glu  <math>\beta</math>-D-xyf         </p>	[59]										
<i>Gleditsia sinensis</i>	 <p data-bbox="807 889 826 910"><b>25</b></p> <p data-bbox="788 1157 807 1178"><b>26</b></p> <p data-bbox="769 1342 788 1364"><b>27</b></p>	[60]										
<i>Saussurea lappa</i>	 <p data-bbox="683 1583 751 1604"><b>28</b> R = FG1</p> <table data-bbox="628 1732 724 1817"> <thead> <tr> <th>R</th> <th>R1</th> </tr> </thead> <tbody> <tr> <td><b>28</b> FG1</td> <td>-</td> </tr> <tr> <td><b>29</b> FG1</td> <td>FG<sub>2</sub></td> </tr> <tr> <td><b>30</b> FG1</td> <td>FG<sub>3</sub></td> </tr> <tr> <td><b>31</b> FG1</td> <td>FG<sub>4</sub></td> </tr> </tbody> </table>	R	R1	<b>28</b> FG1	-	<b>29</b> FG1	FG <sub>2</sub>	<b>30</b> FG1	FG <sub>3</sub>	<b>31</b> FG1	FG <sub>4</sub>	[62]
R	R1											
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<b>29</b> FG1	FG <sub>2</sub>											
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<b>31</b> FG1	FG <sub>4</sub>											

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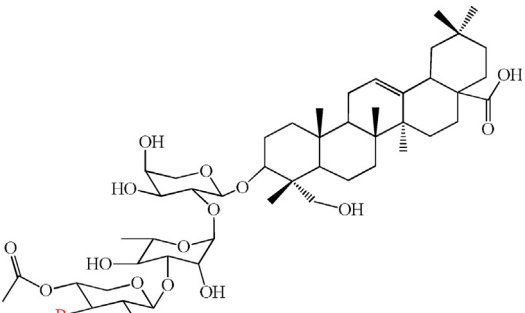
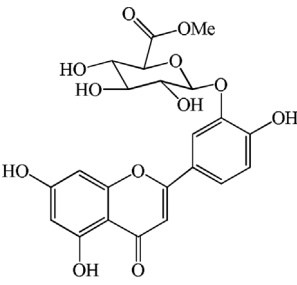
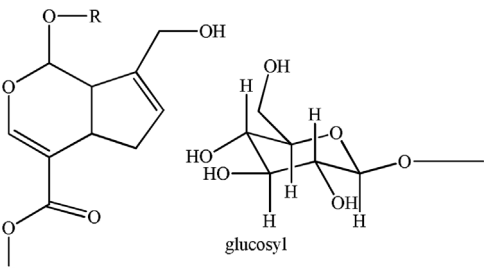
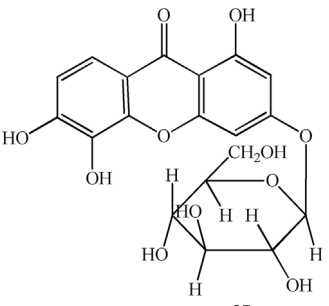
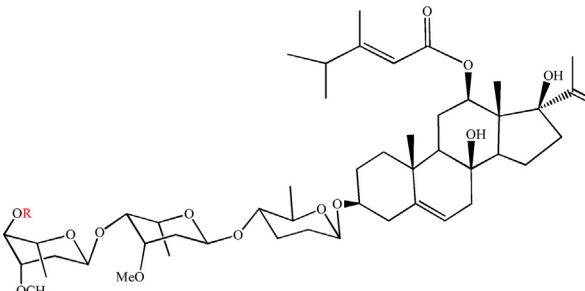
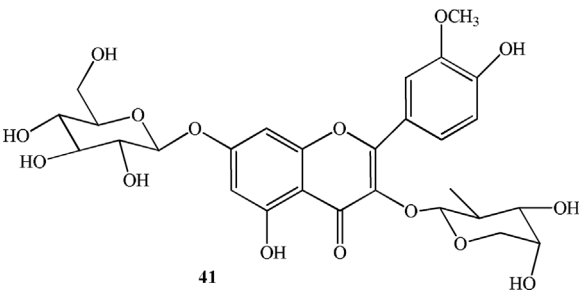
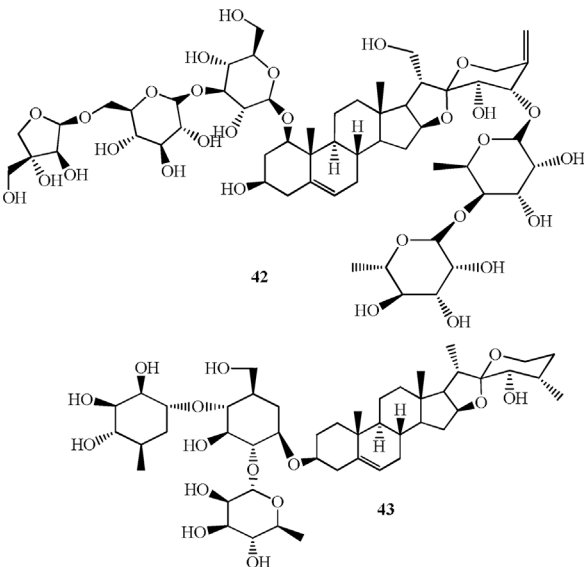
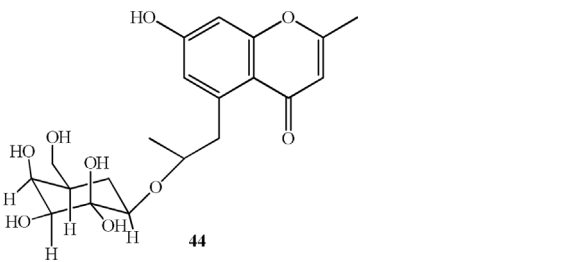
Plant name	Chemical Structure	Reference
<i>Sapindus saponaria</i>	 <p data-bbox="826 542 941 585"> <b>32</b> R = OH  <b>33</b> R = OAc         </p>	[63]
<i>Vitex negundo</i>	 <p data-bbox="654 915 678 946"><b>34</b></p>	[64]
<i>Gardenia jasminoides</i>	 <p data-bbox="790 1202 869 1234">glucosyl</p> <p data-bbox="622 1287 766 1330"> <b>35</b> = R = glucosyl  <b>36</b> = R = H         </p>	[65]
<i>Peperomia pellucida</i>	 <p data-bbox="798 1659 821 1685"><b>37</b></p>	[66]

Table 1 (Continued)

Plant name	Chemical Structure	Reference
<i>Cynanchum wilfordii</i>	 <p data-bbox="742 512 975 576"> <b>38 = R = H</b>  <b>39 = R = <math>\alpha</math>-L-glucose-<math>\beta</math>-D-glucose</b>  <b>40 = R = <math>\beta</math>-D-glucose</b> </p>	[67]
<i>Callianthemum taipaicum</i>	 <p data-bbox="742 880 762 902">41</p>	[68]
<i>Trillium govanianum</i>	 <p data-bbox="794 1208 815 1229">42</p> <p data-bbox="922 1442 943 1464">43</p>	[69]
<i>Acacia ataxacantha</i>	 <p data-bbox="742 1783 762 1804">44</p>	[70]





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 sulphhydryl 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- $\alpha$ -l-arabinoside-7-O- $\beta$ -D-glucoside, from *Callianthemum taipaicum*. This glycoside showed antifungal activity against *Rhizoctonia cerealis* (MIC 1.92 mg/mL), *Botrytis cinerea* (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  $\mu$ g/mL) and borassoside E pennogenin (MIC = 2.5  $\mu$ g/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  $\mu$ g/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 phyto glycosides

Researchers around the world have extensively investigated the underlying mechanisms for antifungal sensitivity of phyto glycosides (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 *Hyocymus 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

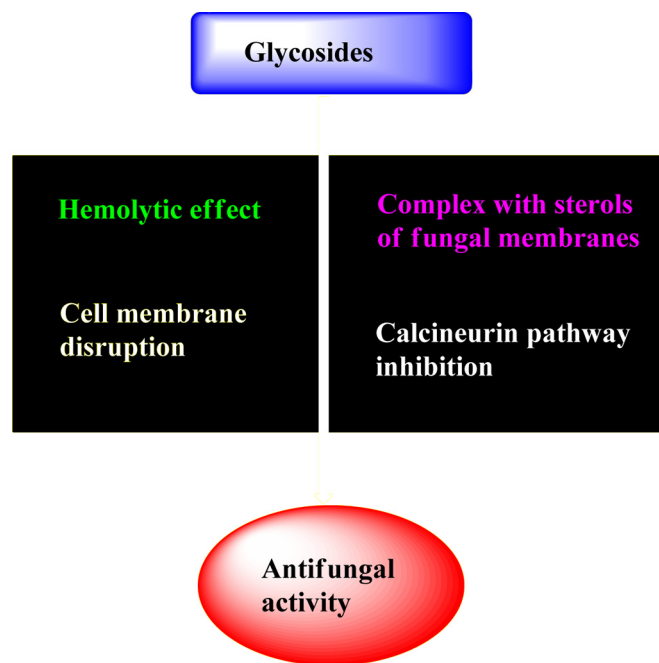


Fig. 1. Proposed antifungal mechanisms of plant glycosides.

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 serine/threonine 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 phyto glycosides as antifungal agents revealed 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 role in overall new drug discovery. The major advantage of such techniques is theoretical modification of results and thus desirable 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 pharmaceutical 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- $\alpha$ -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.

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