Biomedicine & Pharmacotherapy 93 (2017) 498–509

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

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

Haroon Khan[a,*,1], Ziyad Khan[a,1], Surriya Amin[b,1], Yahia Nasser Mabkhot[c,1], Mohammad S. Mubarak[d,*,1], Taibi Ben Hadda[e,1], Francesco Maione[f,1]

[a] Department of Pharmacy, Abdul Wali Khan University Mardan, 23200, Pakistan
[b] Department of Botany, Islamia College University Peshawar, Pakistan
[c] Department of Chemistry, College of Science, King Saud University, P. O. Box 2455, Riyadh-11451, Saudi Arabia
[d] Department of Chemistry, The University of Jordan, Amman 11942, Jordan
[e] LCM Laboratory, University of Mohammed 1st, Faculty of Sciences, Oujda 60000, Morocco
[f] Department of Pharmacy, University of Naples Federico II, Via Domenico Montesano 49, 80031, Naples, Italy

ARTICLE INFO

Article history:
Received 2 May 2017
Received in revised form 16 June 2017
Accepted 20 June 2017

Keywords:
Fungal infections
Natural glycosides
Alternative antifungal therapy

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.

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

* Corresponding authors.
E-mail addresses: hkdr2006@gmail.com (H. Khan), mmubarak@ju.edu.jo (M.S. Mubarak).
[1] Authors contributed equally to this work.

http://dx.doi.org/10.1016/j.biopha.2017.06.077
0753-3322/

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