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BACTERIAL PROTEINS WITH ANTI-*CANDIDA* PROPERTY AND THEIR MODE OF ACTION: A REVIEW.

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ABSTRACT

Due to the undesirable effects of several anti-*Candida* agents and increase in development of drug resistance in *Candida* species, it is necessary to find new safe and effective anti-*Candida* agents. Natural products are best choice to screen new compounds due to various reasons. Plants and fungi are traditionally used and extensively researched for anti-*Candida* compounds. Many synthetic variants of these molecules are used in the market to compact many diseases. Many bacteria are reported for their ability to produce anti-*Candida* compounds. These compounds fall into mainly three categories, ie. Bacteriocins, biosurfactants and anti-*Candida* enzymes. Many of these compounds have therapeutic potential and are safe due to their specificity. Moreover, due to their diversity it is possible to find new molecules from bacterial kingdom. This review is a compilation of information on proteinaceous anti-*Candida* compounds from bacterial origin.

KEYWORDS: Candidiasis, Anti-*Candida* proteins, Secondary metabolite, Bacteriocin and Biosurfactant.

INTRODUCTION

Candida is a ubiquitous microflora of human body, usually seen respiratory, gastrointestinal, reproductive tracts, skin and nails of most healthy people.[1, 2] Although harmless, under various circumstances such as immune-compromised conditions, cancer, diabetics, increased estrogen levels in the body and long term antibiotic usage, *Candida* can cause infection. Candidiasis is a common yeast infection caused by *Candida*. Fig. 1 depicts Fig. 1 depicts

different types of candidiasis. Until recently, *Candida* infection was thought to be caused by *Candida albicans*, however, in the last years other species, such as *C. tropicalis, C. parapsilosis, C .krusei, C. glabrata* and also some less-prominent species like *C. famata, C. guilliermondii, C. rugosa, C. lusitaniae, C. inconspicua, C. kefyr, C. dubliniensis, and C. norvegensis* have been found to be important causes of candidiasis. [1] The diseases spectrum caused by *Candida* consists of superficial and invasive *Candida* infections. Infection of the mucous membranes are associated with defects in cellular immunity such as the depletion of CD4-positive T-helper cells in immunocompromised patients. Invasive candidosis is a serious, potentially lethal disease. Studies from the early 1980s demonstrated mortality rates of up to 70 %.[3]

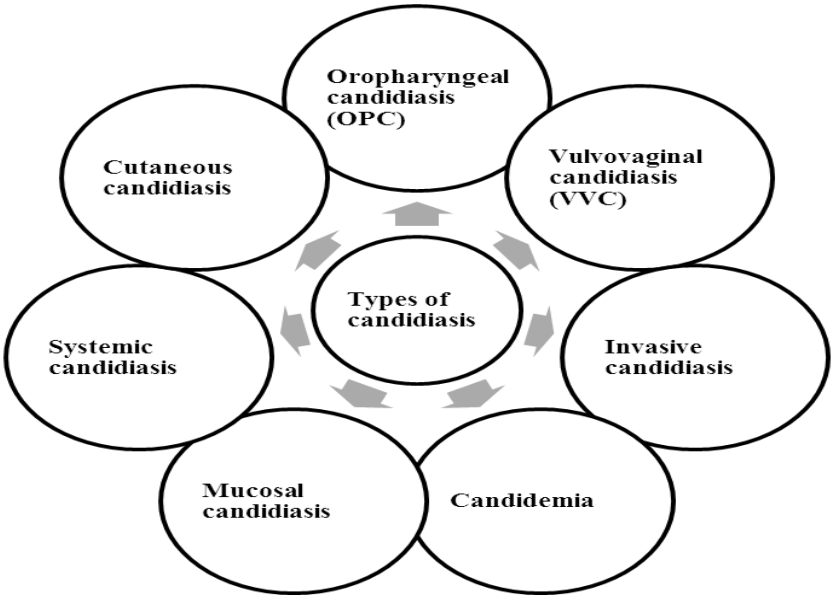

Fig.1. Major types of candidiasis. [2, 4]

Common mode of treatment for candidiasis is the application of azole derivatives, polyenes, fluoropyrimidines and echinocandins. Azole derivatives are the major drugs used in candidiasis, they act by interfering with biosynthesis of ergosterol in the fungal cell membrane.[5] Where as polyenes induces the formation of porin channels in association with ergosterol and destabilizes the trans-membrane potential. Echinocandins targets the β 1-3-D glucan, which is essential for the structure and function of the fungal cell wall. Fluoropyrimidines interferes with DNA and RNA synthesis in *Candida* species.

Recently, due to wide spread of immuno compromized diseases and over proscription of various anti-*Candida* drugs, *Candida* species developed various mechanisms of drug

resistance.[5] Four mechanisms of drug resistance have been reported in the case of azole resistance in *Candida*; (i) induction of efflux pumps that leads to reduction of azole concentration inside the cell, (ii) development of bypass pathways, (iii) up regulation of efflux pumps encoded by either *CDR* or *MDR* genes and (iv) mutations in the target enzyme (ERG11) gene.[6] Mechanisms of polyenes resistance in *Candida* species is due to the alteration of drug target site in membrane ergosterol.[7]

Although rare, increase in MICs to amphotericin-B by *C. glabrata*, *C. krusei* and *C. lusitaniae* have been reported by Pfaller et al.,[5] which implies the emergence of drug resistance to polyenes.[8] Like polyenes, resistance to echinocandins also includes alteration in drug target site in membrane ergosterol.[7]

Resistance of *Candida* species to 5-fluorocytosine (5-FC) is mediated by enzymatic modifications that either interferes with drug uptake into the cell or the conversion of 5-FC to 5-fluorouracil or 5-fluorouracil to 5-fluorouridine monophosphate.[7] In addition, continuous use of anti-*Candida* drugs also causes undesirable side effects and show drug-drug interactions. Relapse of *Candida* infection is also a major problem associated with *Candida* treatment.[9,10]

This scenario of limited class of anti-fungal drugs, resistance, relapse and high cost of treatment necessitate finding of new anti-fungal drugs. Common method used in antibiotic treatment is to modify existing drug to avoid resistance mechanisms, however, the rate at which the pathogen develops resistance against these new drugs are alarming. These directs the scientists to find a classical way of drug discovery to find a classical way of drug discovery from natural sources with a new and effective drug to tackle the problems with drugs which already exist.[11]

Drugs from natural products (NP's) can be the best alternative to existing synthetic antifungal drugs, due to difficulty in acquiring resistance against NP's for microbial pathogens as chemical scaffolds of natural products are very complex and are created by microbial organisms in order to interact with the diversity of biological targets in the environment. Indeed, approximately 80% of all available clinically used antibiotics are directly (or indirectly) derived from NP's, whereas from last 30 years very few first-in-class synthetic antifungal drugs are reported.[12, 13]

Many reports have shown that natural products isolated from different sources like plants, bacteria and fungi are effective inhibitor against *Candida* species with scope as new antifungal drug.[14–16]

Anti-*Candid*a products from plants include essential oils, terpenoids, saponins, phenolic compounds and alkaloids etc. which inhibits *Candida* species by various mechanisms.[17] Plant based anti-fungal compounds have been reviewed by Palande et al.[18] Berberine is a type of alkaloid which intercalates with *Candida* DNA which in turn inhibits protein biosynthesis causing cell death.[19] Linalool, Carvacrol, thymol and borneol are the compounds found in essential oil.[17]

Linalool inhibits H^+ extrusion by the proton pumps, Carvacrol and thymol inhibits ergosterol biosynthesis and borneol disrupts the membrane integrity in *Candida*.[17,20,21] Saponin act by disrupting the membrane integrity of *Candida* cells.[17] Terpinen-4-ol is a terpenoids which alters membrane properties, inhibits respiration and germ tube formation in *Candida.*[22] Phenolic compounds like gingerol disrupts the membrane integrity of *Candida*.[23]

Fungi are well known for their production of multiple types of secondary metabolites and many reports showed that these secondary metabolites have anti-*Candida* property. For example, six compounds viz. cerulenin, arundifungin, sphaeropsidin A, 5-(1,3-butadiene-1-yl)-3-(propene-1-yl)-2-(5H)-furanone, ascosteroside and derivative of 5- ascosteroside B, which were isolated from five species of Coprophilous fungi showed effective inhibition against *C. albicans*.[15] Antifungal agents like echinocandin and pneumocandins (lipopeptides) isolated from fungi have potent anti-*Candida* activity bacause these agents are 1-3-β-D glucan synthase inhibitors.[24]

Several species of bacteria (*Bacillus subtillis, Bacillus mojavensis, Bacillus licheniformis, Lactobacillus plantarum, Lactobacillus amyloliquifaciens* and *Enterococcus* etc.) are known for their ability to inhibit *Candida*. Anti-*Candida* proteins produced by bacteria are majorly of two type; (i) proteins and (ii) proteins with conjugated lipids.

Natural anti-*Candida* compounds from plants and fungi are reviewed by many authors; however, natural product from bacteria other than bacteriocin is not well documented. Hence, this review will focus on the anti-*Candida* molecules especially proteins produced by bacteria and their mechanism of action against *Candida* species.

ANTI-*CANDIDA* PROTEINS FROM BACTERIA

Anti-*candida* proteins produced by bacteria can be generally grouped into bacteriocins, biosurfactants and anti-*Candida* enzymes. Bacteriocins are ribosomally synthesized peptides and biosurfactants are synthesized non-ribosomally.[26]

Bacteriocin

Bacteriocins are sited as potential alternative for commonly used anti-fungal compounds. By definition bacteriocins are small ribosomal peptide secreted by bacteria against closely related species.[25] However, many bacteriocin produced by normal human flora can also inhibit *Candida* since they share a common niche, thus bacteriocins give a competitive edge over the pathogen. Bacteriocins are extremely heterogeneous group of antibacterial substances, which can be chemically diverse but one unifying property is presence of protein component.

Bacteriocins can be classified into four groups on the basis of their structure and molecular weight. Class I bacteriocins include small lantibiotic (<5 KDa), that contain lanthionine, dehydro-alanine etc. Class II bacteriocins are non-lanthionine containing small peptide (<10 KDa) and they are heat stable. Class III bacteriocins contain heat stable large peptide (>30 KDa) and class IV consisting of complex bacteriocin containing carbohydrate and lipid moieties.[26]

Some anti-*Candida* bacteriocins are proteinaceous in nature but contradictory to that generally accepted definition of bacteriocin given by Klaenhammer,[25] so peptide cannot therefore be defined as a true bacteriocin and known as a bacteriocin like peptides.[27]

Anti-*Candida* activity of well-characterized bacteriocin, Nisin Z has been studied by Lay et al., [28] and proved that Nisin Z can inhibit yeast form as well as transformation from yeast to hyphal form. Formation of hyphal form attributed to the pathogenicity of *Candida*. Worldwide many new compounds are screened for the ability to inhibit Yeast to Mycelia (YM) shift in *Candida albicans* and this class I bacteriocin can be a possible alternative to the existing drugs.

Another important anti-*Candida* bacteriocin is TV 35b, belong to Class IIa, produced by *Lactobacillus pentosus*. It induces membrane potential dissipation, ROS and efflux the ATP from the cells.

Another anti-*Candida* bacteriocin (4.5 kD) from *Bravibacillus brevis* GM100 also belong to class II. As discussed by Sharma et al., two bacteriocin peptides, plantaricin E and F also have anti-*Candida* activity.[29]

The common mode of action of all bacteriocins is to disrupt the cell membrane of *C. albicans*. Bacteriocin and bacteriocin like peptides (BLP) interacts with cell membrane and induces pore formation, which leads to disruption of electrochemical gradient across plasma membrane and increase in membrane permeability. This increase in the membrane permeability brings about the flow of potassium ions from target cells. BLP (bacteriocin like peptide) also decreases the rate of respiration.[30]

Biosurfactants

Biosurfactants are compounds produced by bacteria and mostly accumulated on microbial cell surface, or substrate or excreted in the medium. They are amphiphilic in nature due to hydrophobic and hydrophilic moieties.[31] Hydrophilic moieties can be carbohydrate, amino acid, cyclic peptide, carboxyl acid or alcohol and hydrophobic moiety is either a long chain fatty acid or hydroxyl fatty acid.[32] They can be secondary metabolites and are also important for survival of the producing microorganism.[33]

Biosurfactants such as (i) lipopeptide, (ii) glycolipid, (iii) protein like substances,(iv)fatty acids,(v) neutral lipids and polysaccharide-protein complexes are reported and synthesized by many bacterial species and the production can be controlled by altering the media composition and growth conditions. [34, 35]

Bacterial surfactant is a class of bio-surfactant in nature and represents antiviral, anti-microbial, anti-tumor and anti-adhesive activities.[36, 37] The lipopeptide compounds are synthesized non-ribosomally by a large modular multi-enzyme templates designated as peptide synthatases. Among several categories of biosurfactants, lipopeptide is very interesting because of their high antibiotic potential and surface activities. It can act as a antiviral, antitumor agent and enzyme inhibitor.[38]

Lipopeptides from *Bacillus* species can be classified into mainly three categories of cyclic compounds-surfactin, iturin and fungycin.[39,40] Each family contains a residue with same peptide length, but each residue has different specific position of amino acids. Moreover,

each variant can have several homologous of different length and isomer of fatty acid chain, leading to remarkable structure heterogeneity.[40]

Several bacterially originated natural lipopeptides are already used in clinical application, like Polymixins and its derivatives isolated from *Bacillus polymyxa* and amphomycin isolated from *Streptomyces Canus*.[26]

Syringomycin is also already reported lipodepsipeptide produced by *Pseudomonas syringae*; it binds to ergosterol and increases K+, H+ and Ca+ fluxes which ultimately disrupt membrane potential. Sorenson et al., have reported that Syringomycin E and Syringotoxin B can be used as anti-*Candida* compounds. An oinment with 12% of syringomycin E was effective in controlling vaginal candidiasis in murine model[41]. Nickomycins, another naturally occurring peptidyl nucleoside produced by *Streptomyces tendae* enter into *Candida albicans* cell via dipeptide permease and inhibit chitin synthesis, both *in vitro* and *in vivo*.[42, 41]

Surfactin

Surfactin is a cyclic lipopeptide. There are mainly three types of surfactins, A, B and C, classified according to the differences in amino acid sequence. [33] Surfactin composed of heptapeptide cycle and contains lactone ring system. When comes in contact with *Candida*, due to its amphiphilic nature a hydrophobic interaction occur between surfactin and *Candida* membrane phospholipids. Surfactin further penetrate into membrane, destabilizes it by producing pores.

Iturin : It is also a cyclic lipopeptide. Iturin-A is a potent antifungal lipopeptide with many properties. This family consists of bacillomycin-D, iturin and mycosubtilin out of which iturin displays minimal antibacterial activity but major hemolytic activity.[43]

Mode of action of iturin is somewhat like that of surfactin, due to amphiphilic in nature it interacts with cell membrane and disrupt the membrane integrity. Long acyl chain of iturin can entirely incorporated into cell membrane as compare to short acyl chain which cannot span acros the membrane.

It is reported that in case of iturin like bacillomycin-D, anti-*Candida* activity is directly correlate with length of acyl chain, change in 1-2 carbon in acyl chain can alter 10-15 fold

anti-*Candida* activity.[44] Initial human and animal clinical trial showed that, iturin A can be used as a anti-darmatomycoses with wide spectrum of antifungal and minimum side effects. But unfortunately, bacillomycin L and iturin A have been showed hemolytic activity, and this property can reduce their potential use as anti-*Candida* drugs.[33]

Fungycin

it is a cyclic lipopeptide produce by *Bacillus* species. It contains a β –hydroxy fatty acid with long side chain of 16-19 carbon atoms. This antimicrobial peptide (AMP) is known to exhibit strong fungi-toxic activity specifically against filamentous fungi, inhibiting enzymes aromatase and phospholipase A2.[45, 46] Roy et al., reported that fungicin from *Bacillus thuringiensis* SM1 destabilizes the cell membrane of *C. albicans*.[45]

Mechanism of *Candida* inhibition

There are two methods by which surfactant can inhibit *Candida* growth. In first mechanism, reported by Janek et al.,[47] it prevents the adhesion of *Candida* cells on infection site. It is possible due to the amphiphilic nature of biosurfactants. Anti-adhesive nature of biosurfactant is a useful property for a therapeutic agent since it can prevent colonization of pathogen and hence infection.[45] This mechansim has been proven in the case of pseudofactin-2, a biosurfactant produced by *Pseudomonas fluorescene* BD5 and a glycolipid bio-surfactant from *Bravi bacteriumaereum* MSA-19, which can prevent biofilm formation of *C. albicans* on host cells.[47, 48]

Fracchia et al., also proved that a biosurfactant namely CV8LAC isolated from *Lactobacillus*-CV8LAC strain can inhibit the adherence of *C. albicans* cells on polystyrine plate and can be a potential drug for inhibiting biofilm formation.[49]

In the second mechanism, biosurfactant can adhere on the pathogen cell surface and deteriorate the integrity of cell membrane and also breakdown its nutrition cycle. It is possible due to amphiphilic nature of biosurfactants, fatty acid component of biosurfactant get incorporated into cell membrane and causes an increase in the size of cell membrane. This leads to the change in ultra structure of cell such as ability to interiorize plasma membrane. Moreover, insertion of shorter acyl tail into cell membrane leads to disruption of arrangement of cytoskeleton element which results in detachment of plasma membrane from the cytoplasm.[50, 51]

Anti-*Candida* enzymes

Enzymatic degradation of fungal cell wall through extracellular bacterial Chitinase has implicated as a mechanism of biocontrol by bacterial agent.[52] Generally chitinolytic enzymes are divided into mainly three categories, (a). Exochitinase- it is effective only for the non reducing end of chitin chain, (b) Endochitinase- which hydrolyze internal link between beta 1-4 glycosides and (c) B-N-acetylglucosaminidase-which cleave GlcNAc units sequentially from non-reducing end of substrate.[53] Nickomycins are naturally producing peptides from *Streptomyces tandae* inhibit chitin synthesis in *Candida.*

Reports have already shown anti-*Candida* activity of chitinase isolated from *Streptomyces* N II 1006 and *Streptomyces* sp. 5K10.[54,55]

Mode of action of Chitinase

chitin is a homopolymer of N-acetyl-D-glucosamine linked by β 1-4 glycosidic bond. It is a fibrous strengthening element of fungal cell wall; it provides rigidity through strong hydrogen bonding between adjacent polymers. Thus, polysaccharide and glycosidic bonds is the key for cell wall integrity. So due to chitinolytic tendency of chitinase from various bacterial cells, disruption in glycosidic bond is detrimental to fungal cellular morphology, weakening the cell wall and leading to leakage of cell contents.[56]

A comprehensive list of different bacteria producing different anti-*Candida* proteinaceous compounds is given in the Table 1.

Table 1: Bacteria, their anti-*Candida* compounds and its mode of action against *Candida* species.			
Sr. No.	**Name of Bacterial species / strain**	**anti-*Candida* compounds**	**Mode of action against *Candida* species.**
Bacteriocins			
1.	*Lactobacillus pentosus* 35 b	TV 35 b	It disrupt *Candida* membrane .[57]
2.	*Lactobacillus plantarum* 299V, *Bacillus licheniformis* MKU3.	Bacteriocin	Induces membrane potential disruption in *C. albicans*[58, 59]
3.	*Enterococcus faecalis*	Bacteriocin like peptide	It induces membrane potential dissipation, ROS and efflux the ATP from the cells.[60]
4.	*Enterococcus sanguinicola*	Bacteriocin like substance	It disrupt the electrochemical gradient across the cytoplasmic membrane by pore formation and increases the flow of potassium ions by increasing membrane permeability. It also decreases respiration rate..[61]
5.	*Lactobacillus fermentum CS 57*	Bacteriocin like substance	Disrupts the cell membrane of *Candida*.[62]
6.	*Enterococcus faecium strain LWP760*	Bacteriocin-S760	It disrupts the cell membrane of *C. albicans* and *Candida tropicalis.*.[63]
7.	*Bravibacillus brevis strain GM 100*	Bacteriocin	It has the ability to inhibit *C. tropicalis* by inducing disruption in cell membrane.[64]
8.	*Lactobacillus plantarum sp. TN635*	Bac TN635 (Bacteriocin)	It has the ability to inhibit both *C. albicans* and *C. tropicalis* by inducing disruption in cell membrane.[65]
9.	*Lactobacillus fermentum L23*	Bacteriocin L23	It inhibits both *C. albicans* and *C. glabrata* by same mode of action like other bacteriocin.[66]
10.	*Lactococcus lactis*	Nisin Z	It inhibits transformation from yeast to hyphae in *Candida* albicans.[28]
11.	*Lactobacillus plantarum*	Plantaricin peptides.	Enhances the production of ROS (reactive oxygen species) as well as damages cell membrane or may induce release of potassium (k).[29]
Biosurfactants			

12.	*Bacillus amyloliquifaciens* / anti- CA , *Bacillus mojavensis* (accession number- KC 3417)	Surfactin Iturin Fungicin	These peptides like Surfactin believed to kill target cells by destroying their membranes, thereby mimicking the action of porins.[67, 68]
13.	*Bacillus licheniformis* strain M104	Biosurfactant (a lipopeptide)	Adhering property of biosurfactant to cell membrane of target cells causes deterioration in integrity of cell membrane and also breaks down the nutrition cycle.[27]
14.	*Lactobacillus*- CV8LAC	(CV8LAC) a Biosurfactant	Inhibits the adhesion of *Candida* cells to surface and thereby inhibit the biofilm formation.[49]
15.	*Bacillus amyloliquifaciens* strain AR2	Cyclic- lipopeptide (Biosurfactant)	It prevents biofilm formation in *Candida* by following ways- It alters cell surface hydrophobicity or hinders germ tube formation or can reduce the mRNA expression of hyphae specific genes – HWP1 and ASL3.[69]
16.	*Bravibacterium aereum* MSA-19	Glycolipid (Biosurfactant)	It prevents the biofilm formation in *Candida*, because it is a anti-adhesive compound and it prevents attachment of pilli and flagella to surface.[48]
17.	*Bacillus thuringiensis strain SM1*	Fungycin like peptide	It disrupts cell membrane of *C. albicans.*[45]
18.	*Pseudomonas fluorescene BD5*	Pseudofactin II (a cyclic lipopeptide bacteriocin)	It is an anti-adhesive compound, so it interferes with the microbial adhesion and desorption processes and ultimately prevents the biofilm formation in *Candida* species because adhesion to surface is first step in biofilm formation.[47]
19.	*Bacillus subtillis* / B38	Bacillomycin –D like lipopeptide	It works by interacting with cytoplasmic membrane causing pore formation in membrane.[44]
Others			
20.	*Streptomyces* N II1006 and *Streptomyces* sp. 5k10	Chitinase and beta 1-4 glucanase as a secondary metabolites	These compounds inhibit *Candida* cell wall.[54,55]
21.	*Lactobacillus plantarum* strain LR/14	Proteinaceous metabolite	It induces the disruption of cell membrane as well as leakage of intracellular components like K, ATP. It also reduces biofilm formation in *Candida.*[70]

22.	*Bacillus aneurinolyticus*	Tyrocidines(a cyclic lipopeptide)	It inhibits the biofilm formation by disrupting the membrane integrity of mature *C. albicans* biofilm cells. It also has activity against planktonic *C. albicans* cells in which it induces ROS formation in *Candida*.[71]
23.	*Bacillus licheniformis D1*	BL-DZ1(a extracellular protein	It is a secondary metabolite which prevents biofilm formation in *Candida* and also has ability to disperse pre-formed biofilm.[72]
24.	*Pseudomonas aeruginosa*	Pyocyanin (a toxin compound)	It prevents the biofilm formation in both *C. albicans* and *C. tropicalis.*[73]

CONCLUSION

Nowadays, over use of commercially available antimicrobial drugs caused drug resistance in many human pathogenic microorganisms. The resistance adaptation properties of *Candida* species is a major health concerns and it force scientist to discover new effective antifungal agents. Natural products have been proven as the best choice for new molecules and important antifungal agents such as polyenes, aureobasidins, echinocandins and sordarinsare produced natural in origin.

Bacteria have been a key source for the discovery of new drugs and can provide a potential antifungal lead against the resistance strains of *C. albicans.*

Fight to control *Candida* infection has led to the identification of many proteins from bacterial kingdom. They can be grouped into three category, bacteriocins, bio surfactants and anti-*Candida* enzymes. Among these three, bacteriocins have been studied in details for its use as therapeutic agents. Bacteriocins are much preferred anti-*Candida* therapeutic molecules due to its small size, specificity and narrow range of action. In the case of biosurfactants, they inhibit the colonization of the pathogen whereas specificity and toxicity are major concern. Among the enzymes, chitinase is the molecule

Although many proteins with anti-*Candida* activity are known, bacterial kingdom due to its vast diversity still remains as an untapped source of compounds with anti-*Candida* activity. However, with logical exploration of various habitats and studies using modern techniques it is possible to identify and develop new therapeutics.

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