WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 14, 426-438. Review Article ISSN 2277– 7105

A PROMISING APPLICATION OF BACTERIOCIN AGAINST FUNGAL INFECTIONS

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Article Received on
28 May 2018,

Revised on 18 June 2018,
Accepted on 08 July 2018

DOI: 10.20959/wjpr201814-12904

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ABSTRACT

Mycoses are diseases caused by fungi. Mycoses have become a growing problem in modern medical care with the increase in the population of patients with immunodeficiency or undergoing immunosuppressive therapy. The diagnosis of these diseases can be problematic, drug resistance is of great concern and fewer drugs are available compared to bacterial or viral diseases. Fungal infections lead to various diseases that can be Local, superficial, allergic or systemic. For the treatment of fungal infections bacteriocins have very promising candidate as antifungal agent. Bacteriocins are ribosomally synthesized antimicrobial peptides, have traditionally been used as food preservatives, either added or produced by starter cultures during fermentation. In-depth studies of a select few bacteriocins opened exiting new research fields and broadened the application of these antimicrobial peptides. The application of the produced antimicrobial compounds as a natural barrier against fungal pathogens have been proven to be efficient. The present review focus on the bacteriocins unique properties which could be explored and utilized as an antifungal agent

KEYWORDS: Antifungal agents, Bacteriocin, antimicrobial, fungal infections.

INTRODUCTION

Fungal pathogens have an enormous influence on plant and animal life. The pathogens have the extraordinary and frightening impact on food security, and ecosystem disturbancescells.[1] In contrast, the effect fungal infections have on human health is not widely recognized and deaths resulting from these infections are often overlooked. (Table1).

Table 1: Statistics of the 10 most significant invasive fungal infections.

Disease (most common species)	Location	Estimated life –threatening infections	Mortality rates(% in infected populations)
Opportunistic invasive mycoses			
Aspergillosis (Aspergillus fumigatus)	Worldwide	>200,000	30–95
Candidiasis (Candida albicans)	Worldwide	>400,000	46–75
Cryptococcosis (Cryptococcus neoformans)	Worldwide	>1,000,000	20–70
Mucormycosis (Rhizopus oryzae)	Worldwide	>10,000	30–90
Pneumocystis (Pneumocystis jirovecii)	Worldwide	>400,000	20–80
Endemic dimorphic mycoses			
Blastomycosis (Blastomyces dermatitidis)	Midwestern and Atlantic United States	~3,000	<2–68
Coccidioidomycosis (Coccidioides immitis)	Southwestern United States	~25,000	<1–70
Histoplasmosis (Histoplasma capsulatum)	Midwestern United States	~25,000	28–50
Histoplasmosis (Histoplasma capsulatum)	Midwestern United States	~25,000	28–50
Paracoccidioidomycosis (Paracoccidioides brasiliensis)	Brazil	~4,000	5–27
Penicilliosi Penicillium marneffei	Southeast Asia	>8,000	2–75

Of particular concern is the high rate of mortality associated with invasive fungal infections, which often exceeds 50% despite the availability of several antifungal drugs (Table 1). The purpose of this Review is to estimate, from available scattered data, the disease burden caused by these pathogens; describe the types and impact of fungal infections worldwide; and illustrate the bacteriocin role in fungal therapies.

Fungi and Human Diseases

Superficial infections of the skin and nails are the most common fungal diseases in humans and affect ~25%(or ~1.7 billion) of the general population worldwide.[2] These infections are caused primarily by dermatophytes, which give rise to well-known conditions such as

athlete's foot (occurs in 1 in 5 adults), ringworm of the scalp (common in young children and thought to affect 200 million individuals worldwide), and infection of the nails (affects ~10% of the general population worldwide, although this incidence increases with age to ~50% in individuals 70 years and older).[2,3] In world regions with limited health care provision, HIV/AIDS adds nearly 10 million cases of oral thrush and 2 million cases of esophageal fungal infections annually.[4] Influence of fungal infection is worldwide. Invasive fungal infections have an incidence that is much lower than superficial infections, yet invasive diseases are of greater concern because they are associated with unacceptably high mortality rates.

Many species of fungi are responsible for these invasive infections, which kill about one and a half million people every year. In fact, at least as many, if not more, people die from the top 10 invasive fungal diseases (Table 1) than from tuberculosis.[5] or malaria.[6] More than 90% of all reported fungal-related deaths result from species that belong to one of four genera: Cryptococcus, Candida, Aspergillus, and Pneumocystis. However, epidemiological data for fungal infections are notoriously poor because fungal infections are often misdiagnosed and coccidioidomycosis (also sometimes called "valley fever") is the only fungal disease that must be reported to the CDC. The immune system of healthy individuals has effective mechanisms for preventing fungal infections, and the current incidence of invasive diseases is largely a result of substantial escalations over the last few decades in immunosuppressive infections, such as HIV/AIDS, and modern immunosuppressive and invasive medical interventions. Some fungi normally live, in manageable numbers, on the host epithelial surfaces of most healthy humans, but can initiate life-threatening systemic infections in those who are immunocompromised. Candida species are the most common fungal etiological agent of life-threatening invasive infections in patients who (i) are severely immune compromised, (ii) have endured invasive clinical procedures, or (iii) have experienced major trauma, and treatment requires extended stays in intensive care units. Indeed, Candida species are the fourth most common cause of nosocomial (hospital-acquired) bloodstream infections.[7]

The occurrence of disseminated Candida infections has been surveyed frequently in the United States and in many European countries, and variable reported incidences ranging from 2.4 (Norway) to 29 cases (Iowa, United States) per 100,000 inhabitants have been published.[8,17] Aspergillus infections also cause a gradual destructive disease in the lung

called chronic pulmonary aspergillosis (Fig. 1), which complicates numerous pulmonary disorders including tuberculosis, COPD, and the systemic inflammatory disease sarcoidosis.[18] Globally, millions of susceptible individuals develop pulmonary and nasal allergies to A. fumigatus and other airborne fungal particles. Severe asthma is linked to fungal allergy and A. fumigatus colonization (or infection) of the airway, principally in adults, but also in children.[19,21] Another common respiratory opportunistic pathogen is Pneumocystis jirovecii, which causes P. jirovecii pneumonia (PJP or PCP) in individuals with impaired immunity, especially those suffering from HIV/ AIDS; in fact, PCP is an AIDS-defining disease.[22] Because of diagnostic inadequacies, the world wide incidence of PCP is unclear, but it is likely to exceed 400,000 cases per year with mortality rates higher than 13% (that is, more than 52,000 deaths per year) andpossibly as high as 80%.[23,24] Fungi also contribute to several other notable diseases, including infection-related blindness and the debilitating and disfiguring chronic subcutaneous infections. Fungal keratitides (infections of the cornea) are notable for their frequency (~1 million new fungal eye infections annually worldwide) and their contribution to blindness, particularly in Asia and Africa.[25] The subcutaneousmycoses are generally uncommon and include chromoblastomycosis (Fig. 1), sporotrichosis, Madura foot (eumycetoma), and the fortunately rare entomophthoramycosis.

Bacteriocin

Bacteriocins comprise a huge family of ribosomally synthesized peptides that have antibacterial activity towards closely related strains.[25,26] Although there are an increasing number of bacteriocins reported to have broad range antimicrobial activity.[27,28] These antimicrobial peptides are also colourless, odourless and tasteless, which further enhance their potential usefulness. Despite the long history of bacteriocin use, there have been no reports on the development of resistant bacteria. One possible reason is that bacteriocins have a fast acting mechanism, which forms pores in the target membrane of bacteria, even at extremely low concentrations. They are also easily degraded by proteolytic enzymes due to their proteinaceous nature.

With the discovery of new bacteriocins that have unique characteristics, it has become apparent that they are a very diverse and heterogeneous group of compounds. Over the years, various schemes have been suggested to classify bacteriocins from Gram-positive bacteria including LAB.[29,32] Cotter *et al*. (2005) suggested a more radical modification of the previous classification scheme.[33] According to this scheme, bacteriocins are grouped into

just two categorie. The lantibiotics (class I) and non-lanthionine-containing bacteriocins (class II), as opposed to the four classes of the Klaenhammer classification scheme.[34] The most notable change in this scheme is that it reclassified the class III bacteriocins as bacteriolysins, since they are lytic enzymes rather than peptides. Recently, although this classification scheme was broadly agreed with, Heng *et al*. (2007) suggested a further modification in which circular bacteriocins should be grouped as a different class.[35] Class I bacteriocins or lantibiotics (lanthionine-containing antibiotics) are small peptides (<5 kDa) that possess unusual post-translationally modified residues such as lanthionine or 3-methyllanthionine. These unusual residues form covalent bonds between amino acids, which result in internal "rings" and give lantibiotics their characteristic structural features.[36,37] The most extensively studied bacteriocin, nisin A and its variants are the main representatives of lantibiotics. Class II bacteriocins, or the non-lantibiotics, are the most naturally occurring bacteriocins. They are small (<10 kDa), heat-stable, non-lanthionine-containing peptides, which, unlike lantibiotics do not undergo extensive post-translational modification. This group can be further subdivided into four subclasses: "pediocin-like" bacteriocins (class IIa), two-component bacteriocins (class IIb), circular bacteriocins (class IIc), and unmodified, linear, non-pediocin-like bacteriocins (class IId).[38]

Biology of bacteriocins

Bacteriocin production is widespread among bacteria. It has been suggested that the majority of bacterial species synthesize bacteriocins.[35] This is because their biosynthetic machineries are relatively simple and are often associated with transferable elements such as conjugative transposons or plasmids.[31] As highlighted earlier, bacteriocins are ribosomally synthesized peptides. Genes related to bacteriocin biosynthesis are generally clustered, and are encoded on plasmids, chromosome and/ or transposons with minimum genetic machinery consisting of structural cognate immunity genes.[29] Bacteriocins are usually synthesized as biologically inactive prepeptides that include an N-terminal leader peptide attached to the C-terminal propeptide.[34] The leader peptide: (i) serves as a recognition site which directs the prepeptide towards maturation and transport proteins, (ii) protects the producer strain by keeping the bacteriocin in an inactive state while it is inside the producer strain, and (iii) interacts with the propeptide domain to ensure it is in a suitable conformation for enzyme-substrate interaction of the modification machinery.[36,38]

Bacteriocin biosynthesis begins with translation of the prepeptide, which consists of a leader peptide and a modifiable propeptide moiety. The prepeptide then undergoes modification, following which the modified prepeptide translocates across the cytoplasmic membrane and the leader peptide is cleaved proteolytically by specific enzymes. Genes encoding immunity proteins, as well as proteins involved in the regulation of its production, are normally located in a cluster around the bacteriocin structural gene. . However, there are a growing number of newly reported bacteriocins that lack leader sequences; these are of interest as they are active immediately after translation.[39,41]

Mode of action of bacteriocin

Due to the great variety of their chemical structures, bacteriocins affect different essential functions of the living cell, but most of them act by forming membrane channels or pores that destroy the energy potential of sensitive cells.[42,43] This could be explained by Klaenhammer's class IIc group on the basis of their chemical structure and properties. The current mechanistic hypothesis to explain the mode of action of bacteriocins belonging to this class includes electrostatic binding of the antibiotic to the target membrane mediated by a putative membrane-bound receptor molecue.[44] Although the necessity of this specific receptor is still controversial.[45,46] The hypothetical receptor would be responsible for the recognition of the YGNGV anti-listerial motif present in these peptides.

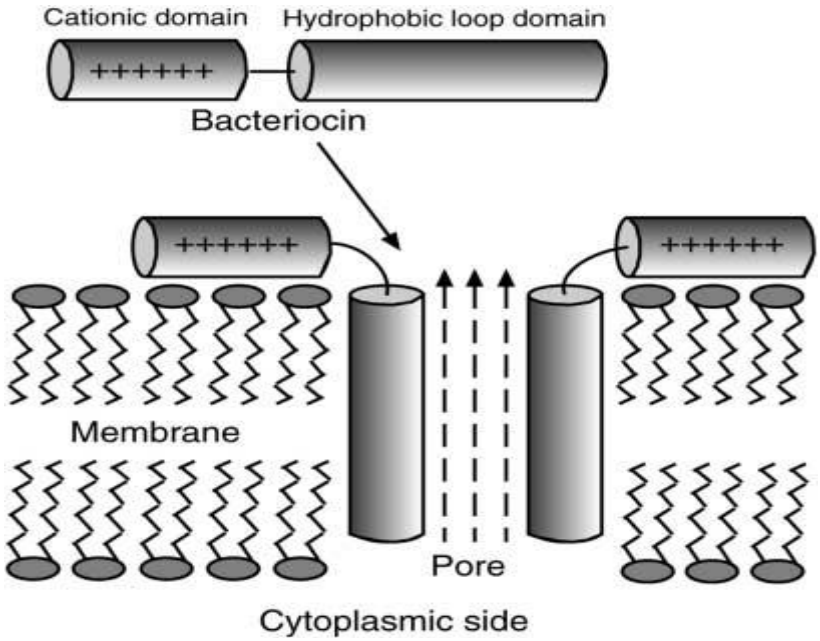

Fig. 1: Mode of action of Bacteriocin.

Application of bacteriocin as an antifungal agent

Antifungal drugs currently used for the treatment of *Candida* infections include polyenes, azoles, echinocandins, allyamines, and flucytosine. These drugs exert either fungicidal or fungistatic activities by interfering with essential processes.[47] Intensive prophylactic and therapeutic uses of antifungal agents have selected for drug-resistant strains.[48,49] Moreover, the limited arsenal of antifungal drugs is further compromised by severe side effects in patients and the emergence of species refractory to conventionally used agents.[50] There is a need to develop new antifungals and to explore novel therapeutic approaches to treat *Candida* infections. To widen the repertoire of antifungal drugs, targets that differ from those of conventional drugs have to be identified. Recently, targeting virulence rather than essential processes has been postulated as a new paradigm for the development of antifungal agents, following the successful development of drugs targeting bacterial virulence in antimicrobial therapy.[51,52] Thus, instead of being killed, a pathogen is maintained in a harmless form by blocking virulence attributes that contribute to its pathogenicity. Moreover, resistance to drugs thattarget virulence instead of growth is less likely to develop, given that selective pressure is reduced on nonessential targets that are required only to colonize host environments.[53] In *C.albicans*, virulence factors that are eligible as targets for the development of new antifungal drugs have been reviewed recently and include secreted aspartic proteases, phospholipases, calcineurin, inositol phosphoryl ceramide synthase, and elastase.[54] In addition to farnesol, *C. albicans* secretes other autoregulatory molecules that influence the Y-H transition.[55,56] Thefusel alcohols 2-phenylethanol and tryptophol were the first molecules reported to inhibit hyphal growth. Yet, these molecules are not QS molecules, given that they are inhibitory at concentrations the yeast cannot produce naturally. An unknown substance termed MARS (morphogenic autoregulatory substance), isoamyl alcohol, and *E*-nerolidol have also been shown to possess hypha-inhibiting activities.[57] As a commensal organism of the mucosal microbiota and a pathogen in different host niches, *C. albicans* encounters microorganisms of the endogenous microflora as well as several opportunistic pathogens. A number of bacteria and yeasts have been reported to secrete molecules that influence the Y-H transition. *Pseudomonas aeruginosa* secretes the 3-oxo-C12-acyl homoserine lactone (3OC12HSL), a 12-carbon backbone molecule structurally related to farnesol, which inhibited the Y-H transition induced in *N*-acetylglucosamine-containing mediumand caused filaments to revert to the yeast morphology.[58] Similar in structure to farnesol and farnesoic acid, dodecanol and three other QS molecules produced by *Xanthomonascampestris*, *Burkholderia cenocepacia*, and *Streptococcus mutans* also exerted

hypha-inhibiting activities.[59] Additionally, *P.aeruginosa* also had an inhibitory effect on *C. albicans* growth *invitro*, in burn wounds, and in the lungs of patients with cystic fibrosis.[60] Pyocyanin, phospholipase C, and phenazines were the molecules responsible for this inhibitory effect.[61] Interestingly, the antifungal activity of *P. aeruginosa* was specifically targeted toward hyphal cells, as bacteria were shown to attach to and kill fungal filaments only. In complex microbial communities, molecules mediate interspecies interactions.[62] For instance, in the presence of 3OC12HSL, *C. albicans* may block hyphal development as a means to escape being killed by *P. aeruginosa*. Conversely, hypha-inducing molecules may mediate synergistic interactions between bacteria and *C. albicans* by promoting biofilm formationand invasion.[63] To circumvent this impediment, small molecules that modulate the Y-H transition in *C. albicans* without affecting cellular growth should be evaluated for their therapeutic potential in various infection models. More data are needed to determine whether or not targeting the Y-H transition constitutes a sound therapeutic strategy to treat *Candida* infections.

CONCLUSION

The effectiveness of bacteriocins as food preservatives is well demonstrated. Though nisin is the only purified bacteriocin used commercially, others such as pediocin, have application in food systems. Their synthesis and mode of action distinguish them from clinical antibiotics. Additionally, organisms that show resistance to antibiotics is generally not cross-resistant with bacteriocins, and unlike antibiotic resistance, bacteriocin resistance is not usually genetically determined. To treat fungal infections there are positive results from many research studies. To circumvent this impediment, small molecules that modulate the Y-H transition in fungi without affecting cellular growth should be evaluated for their therapeutic potential in various infection models and bacteriocin could be considered as a potential candidate as an antifungal agent.

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