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REVIEW ARTICLE

Human Antifungal Agents Originated from the Actinobacteria: Review

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ABSTRACT
Actinobacteria have striking applications in the treatment of human fungal infections. Many antifungal moieties produced by actinobacteria are in use along with the antifungal peptides and metabolites. For example, Streptomyces nodosus produces Amphotericin B. However, this area has been inadequately studied although sufficient work has been conducted regarding actinobacterial activity against phytopathogenic fungi and many antifungal actinobacteria are waiting for their discovery. In this review, merits and demerits of the proposed area have been analyzed to support human health.
Keywords: *Actinobacteria, amphotericin B, antifungal peptides, pathogenic fungi*

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INTRODUCTION

Human antifungal agents are used to treat fungal infections, which have been increased in case of humans in last 30 years (Lass-Flörl) [1] that are challenging for a treatment due to their eukaryotic nature. Antifungal antibiotics have a considerable role in controlling the diseases caused by fungi although they are very less (S.Usha Nandhini et al. [2]. Actinobacteria produce antifungal agents in the nature (Spadari CD, et al [3] and Alpana Bharti et al. [4] reported that Garhwal region of Uttarakhand, India produce many antifungal metabolites. For example, the genus *Streptomyces* produces antifungal secondary metabolites (Dongli L, et al. [5], Zhao J et al. [6], Doumbou et. al., [7]). There are many antifungal agents that are originated from the actinobacteria. For example, Binod Lekhak et al. [8] isolated the actinobacteria from Soil of Nepal that inhibits growth of *Candida albicans*, a human pathogenic fungus. Actinomycetes originated from soil reveal antifungal activity (Tinatin and Nuzrat [9]. However, all of them have been not discovered yet and many of the antifungal agents produced by them are needed to be discovered. Wide range of studies have been conducted on the phytopathogenic fungi treatment using actinobacteria but very less work has been conducted for human pathogenic fungi treatment using the actinobacteria. In turn, in the presented review, we have investigated the current status of antifungal agent production by the organism under study.

ANTIGUNGAL AGENTS PRODUCED BY ACTINOBACTERIA

Amphotericin B was first time isolated in 1955 from *Streptomyces nodosus* (Velázquez L and Farmacología B. [10]). Additionally, actinomytes produce antifungal peptides (table 1). Zhang D et al. [11] reported that actinomycetes have potential to produce the antifungal peptides (table 1) but authors never reported the names of actinobacteria producing such proteins. This work has opened new doors for the future researcher to investigate species of actinomycetes producing the antifungal peptides.

Table 1: Antigungal peptides produ ced by actinomycetes (Zhang D et al. [11].

Peptides	Pathogenic fungi
Polyoxins	*Pyricularia oryzae (*Isono K et al. [12], Isono K et al. [13], *Cochliobolus miyabeanus, Physalospora laricina, Cladosporium fulvum, Pellicularia sasakii.*
Nikkomycins	*Glomerella cingulate* [14], Uramoto M.1980 [15], Decker H et al.[16]) *Alternaria mali, Pellicularia sasakii, Pyricularia oryzae, Cochliobolus miyabeanus, Botrytis cinerea, Candida albicans, Sclerotinia cinerea, Colletotrichum lagenarium, Yarrowia lipolytica, Paecilomyces varioti*
Lipopeptin A	*Pyricularia oryzae* (Tsuda K et al. [17], Nishii M et al. [18]), *Colletotrichum lagenarium*
Neopeptins A and B	*Alternaria mali* [19], Satomi T et al. [20], Kim YS et al. 2007 [21]) *Botrytis cinerea, Didymella bryoniae, Magnaporthe grisea, Cladosporium cucumerinum, Colletotrichum lagenarium,*
Globopeptin	*Mucor racemosus KF-223* (Tanaka Y et al. [22], Shrivastava P, Kumar R. et al. [23]) *Pyricularia oryzae KF-180, Botrytis cinerea KF-241, Alternaria kikuchiana KF-185.*
SW-B	*Phytophthora capsici* (Hwang BK et al. [24]) *Magnaporthe grisea, Cladosporium cucumerinum*
Glomecidin	*Glomerella cingulata* (Kunihiro S, Kaneda M., [25]), *Colletotrichum gloeosporioides (Penzig), Colletotrichum lagenarium*
Cyclo (L-leucyl-L-prolyl)	*Glomerella cingulate IFO 9767* (Rhee KH. [26], Rhee K-H et al. [27]), *Mucor ramannianus IAM 6218, Trichophyton mentagrophytes ATCC 18749, Rhizoctonia solani IFO 6218, Trichophyton rubrum ATCC 44766, Pyricularia oryzae IFO 5994, Candida tropicalis, Candida glabrata, Cryptococcus neoformans, Candida albicans*
Coronamycins	*Pythium ultimum, Cryptococcus neoformans, Aphanomyces cochlioides, Phytophthora cinnamomi*
Valinomycin	*Phytophthora capsici, Rhizoctonia solani, Colletotrichum gloeosporioides, Candida albicans, Botrytis cinerea, Magnaporthe grisea*
Cyclothiazomycin B1	*Cochliobolus miyabeanus* (Hashimoto M et al. [28], Mizuhara N *et al. [29]), Botrytis cinerea, Septoria nodorium, Fusarium oxysporum, Fusarium solani, Fusarium avenaceum, Gibberella fujikuroi NBRC 6349, Fusarium sporotrichioides,NBRC 33236, Mucor mucedo IFO 7684, Gibberella zeae NBRC 8850, Myagrus javanicus IFO 4569, Penicillium chrysogenum IFO 4626.*

Actinobacteria produce antifungal substances, which may be used to treat fungal diseases of humans (table 2). Bhosale HJ et al. [30] reported that *Streptomyces indiaensis* SRT-1 produces the antifungal agent but authors have not stated specific antifungal agent and the fungi to which it treats (table 2). This pitfall can be improved by further extensive research on *Streptomyces indiaensis* SRT-1 investigating its antifungal activity. Moreover, Chen et al. [31] and JAKUBIEC-KRZESNIAK K et al. [32] reported that *Streptomyces* sp. produces an antifungal agent that inhibits *C. glabrata*. However, authors failed to report the specific species of *Streptomyces* genus that is used against *C. glabrata.* Additionally, they have not stated the name of produced antifungal agent.

Likewise, Lekhak B et al. [8] revealed that *Nocardiopsis prasina* produces the antifungal agent that may be used to treat *Candida albicans.* In contrast, the authors have not reported the name of produced antifungal agent. To continue, Zothanpuia et al. [33] proposed that *Streptomyces* sp. DST25 produces the agent used to treat *Fusarium udum* infections, where authors failed to report the name of the agent. Likewise, in accordance with Fadhilah QG et al. 2021, *Streptomyces* sp. CACIS-1.5CA is used to treat human pathogenic *Colletotrichum* spp. In contrary to this, the authors never reported the name of produced antifungal agent and exact species of the genus *Colletotrichum*. Bharti A et.al. [4] stated that Saccharothrix sp., *Kitasatospora sp. Streptomyces* sp. may be used to treat fungal infections by ***Trichophyton rubrum,*** *C .albicans, M. canis, M. gypseum, Aspergillus flavus, A. fumigates* but there is no report of the produced antifungal agent. This provides opportunity to the future researchers to elaborate the proposed research.

Table 2: Antifungal agent used against human pathogenic fungi

Antifungal agent	Human pathogenic fungi	Actinobacteria	Reference
Data not available	Data not available	*Streptomyces indiaensis* SRT-1	[30]
Data not available	***Trichophyton rubrum,*** *C .albicans, M. canis, M. gypseum, Aspergillus flavus, A. fumigatus*	*Saccharothrix* sp., *Kitasatospora sp. Streptomyces* sp.	[4]
Urauchimycins	**Candida**	Streptomyces	[34-38]
Sceliphrolactam	*C. albicans*	*Streptomyces* sp.	[39]

(15-glycidylfilipin III; 16α, 17α-epoxyfilipin V; 16β, 17β-epoxyfilipin V	*C. albicans*	*S. lavenduligriseus*	[32]
Data unavailable	*C. glabrata*	*Streptomyces* sp.	**[31, 32]**
Mohangamides A and B	*C. albicans*	*Streptomyces* sp. SNM55	[32]
Neomaclafungin A	*Trichophyton mentagrophytes* ATCC 9533	*Actinoalloteichus* sp. NPS702	[32]
Not Available	*Candida albicans*	*Nocardiopsis prasina*	[8]
2-Isopropyl-5-methyl-1-heptanol and Eicosane	***Candida albicans***	***Streptomyces rubralavendulae***	[2]
Data not available	*Fusarium Udum*	*Streptomyces* sp. DST25	[33]
Data not available	*Colletotrichum* spp.	*Streptomyces* sp. CACIS-1.5CA	[40]

CONCLUSION

The area of antifungal production by actinobacteria for the treatment of fungal pathogenic fungi has been explored inefficiently. There is a great opportunity for the future researchers to explore an area of antifungal agent production against human pathogenic fungi.

AUTHORS' CONTRIBUTIONS

All authors involved in this work have considerable contributions the development of a concept, collection of data, design, and analysis as well as data interpretation. Additionally, they drafted and revised the article critically for valuable intellectual content and they are agreed for submission to the current journal. They permitted the version of a manuscript to be published and they are agreed for the accountability of all aspects of the work.

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CONFLICT OF INTEREST

Authors declare that no conflict of interest exists.

ETHICAL APPROVALS

The work does not involve experiments based on human or animal subjects.

DATA AVAILABILITY

All produced as well as analyzed data are provided in the research article.

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This journal is neutral regarding claims of jurisdiction in the institutional affiliation which is published.

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