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Anti-Fungal Properties of Actinobacters

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ABSTRACT

Increasing use of antifungal agents and long-term therapeutic approaches has led to an increase in the prevalence of fungal species and their resistance to various drugs. The use of biological agents was proposed as a new and less complication way to control diseases. Streptomycetes actinobacteria are considered to be the most potent producers of bioactive compounds such as enzymes, pesticides, herbicides as well as antibiotics in the world. Actinomycete antifungal activity against fungi such as Alternaria mali, C. gloeosporioides, Fusarium oxysporum f.sp. cucumerinum and Rhizoctonia solani are shown. In this study, we aim to represent actinobacteria as a novel therapeutic approach for fungal diseases. Data were collected from in vitro and in vivo clinical studies published in English between 2001 and February 2022 and obtained from the PubMed, Google Scholar, Scopus and Cochrane libraries. Data were collected from clinical, in vitro and in vivo studies published between 2001 and February 2022 in English and were obtained from the PubMed, Google Scholar, Scopus and Cochrane libraries.

Keywords: Actinobacteria; Streptomycetes; Fungi; Anti-Fungal Agents; Bioactive Compounds

Introduction

The incidence of fungal infections in humans has increased significantly in the last 30 years. Today, less attention is paid to antifungal drugs, while fungal diseases have a significant share among infectious diseases [1,2]. compared to Antibacterial agents The number of antifungal compounds approved for use in humans is very limited. Also, the high complication of these drugs and their toxicity testify to the discovery of newer and less complication drugs and treatments [3,4]. The increasing use of antifungal agents in long-term treatment strategies has increased the prevalence of resistant fungal species. Secondary microbial metabolites are the main source of compounds with remarkable chemical structures and strong biological activity [5]. Bacteria belonging to the actinomycete group show several physiological and metabolic properties, such as the production of extracellular enzymes and a variety of secondary metabolites. Their seemingly unlimited ability to produce bioactive compounds makes actinomycetes particularly useful in the development of new drugs [6]. These microorganisms are responsible for producing more than half of the commercially available bioactive compounds, including antibiotics, antifungal and immunosuppressive drugs, antitumor agents, and enzymes. Due to the importance of discovering active compounds with less side effects and stronger against fungi, the aim of this study was to introduce actinomycetes strains with the potential to produce biologically active compounds against fungi and their importance [7,8].

Method of Search

Data were extracted and collected from the PubMed, Google Scholar, Scopus, and Cochrane libraries from the overall term clinical and animal studies published in English between 2001 and February 2022. Search terms included "Fungi" OR "Anti-Fungal" AND "Actinobacteria" OR "Streptomycetes" AND "Bioactive compounds".

Actinobacters

Natural products play a dominant role in the development of new therapeutic agents. Due to their lower side effects than chemical drugs and their greater specificity, actinobacteria represent the most prominent group of microorganisms that produce bioactive compounds that are important in the treatment of many diseases. Most of these molecules are derived from Streptomyces [9]. About 58% of bioproducts are derived from the marine sponge-associated actinobacteria, while the remaining are from the actinobacteria associated with mollusks, mangroves, corals, ascidians, and seaweeds. Moreover, extreme habitats such as caves, deserts or Antarctic ecosystems are recognized as valuable sources of actinomycetes producing novel metabolites of pharmacological importance [8]. Natural product production from the actinobacteria like Actinomadura, Salinispora, Microbacterium, Micrococcus, Saccharothrix, Saccharopolyspora, and Verrucosispora have antibacterial, antifungal, antiparasitic, antimalarial, immunomodulatory, anti-inflammatory, antioxidant, anti-Alzheimer, analgesic, antiarthritic, antifouling, and anticancer activities [10,11].

Actinobacteria Classification

The current arrangement of Actinobacteria is owing to 16S rRNA sequences. In the actinobacteria classification, the subclass and suborders are eliminated and clades used in these terms earlier are elevated to class and order ranks [12]. The phylum of actinobacteria consists of six classes inclusive of Rubrobacteria, Acidimicrobiia, Coriobacteriia, Thermoleophilia, Nitriliruptoria, and Actinobacteria. Actinobacteria comprises 43 families while only 10 families belong to the 5 other classes [13]. Two large clades are found in rRNA gene trees associated with class actinobacteria. The first clade comprises of following orders: Micromonosporales, Actinopolysporales, Jiangellales,Glycomycetales, Corynebacteriales, Propionibacteriales, and Pseudonocardiales while the second clade consists of the orders named: Kineosporiales, Bifidobacteriales, Actinomycetales, and Micrococcales [14].

Class Actinobacteria

Actinomycetales: Order Actinomycetales is associated with the family Actinomycetaceae [15] and this family icludes genra Actinomyces , Actinobaculum, Arcanobacterium, Mobiluncus, and Varibaculum [16]. The related species to the first genus, actinomyces , are Actinomyces bovis and Actinomyces bowdenii, catuli, dentalis, denticolens, gerencseriae, graevenitzii, ruminicola, slackii, howellii, israelii, johnsonii, massiliensis, naeslundii, oricola, oris, radicidentis, urogenitalis, and viscosus in the first clade [17]. The second clade contains Actinomyces canis, cardiffensis, funkei, georgiae, hyovaginalis, meyeri, odontolyticus, radingae, suimastitidis, turicensis, and vaccimaxillae. The last clade is inclusive of Actinomyces marimammalium, hongkongensis, hordeovulneris, and nasicola [18]. Other genras have monophyletic clades. Actinobaculum genra involves species Actinobaculum suis and Actinobaculum massiliense, schaalii, and urinale [19]. Arcanobacterium genre includes Arcanobacterium haemolyticum and Arcanobacterium abortisuis, bernardiae, bialowiezense, bonasi, hippocoleae, phocae, pluranimalium, and pyogenes. Two species Mobiluncus curtisii and Mobiluncus mulieris are related to Mobiluncus genre [20].

Actinopolysporales: Order Actinopolysporales and the corrolated monogeneric family Actinopolysporaceae, comprises of Actinopolyspora mortivallis and Actinopolyspora halophila.

Bifodobacteriales: Order Bifidobacteriales and family Bifidobacteriaceae comprises of genus Bifidobacterium Gardnerella and Aeriscardovia aeriphila, Alloscardovia omnicolens, Metascardovia criceti, Parascardovia denticolens, and Scardovia inopinata.

Catenulisporales: Next order is Catenulisporales, and associated families are Catenulisporaceae and Actinospicaceae in which Catenulisporaceae includes the type species Catenulispora acidiphila and three other related species are Catenulispora rubra, subtropica, and yoronensis and the Actinospicaceae family is inclusive of Actinospica robiniae and Actinospica acidiphila type species.

Corynebacterials: Corynebacteriales order includes the families Corynebacteriaceae, Dietziaceae, Mycobacteriaceae, Nocardiaceae, Segniliparaceae, and Tsukamurellaceae proceed this order in the gene tree. Corynebacteriaceae family contains genus Corynebacterium which contains a large number of species and the type species Turicella otitidis. Dietziaceae is a monogeneric family which encompasses type species Dietziamaris and the related species. Mycobacteriaceae family is a monogeneric , well-defined in the gene tree. It is known for mycolic acids existence and its carbon atoms and the dihydrogenated menaquinones with nine isoprene units [21]. Family Nocardiaceae is paraphyletic and is asscoaited with seven genera however, in the previous tree , the family only consists of Nocardia and Rhodococcus genra [22]. Segniliparaceae family is monogeneric and it is represented by type species Segniliparus rugosus and Segniliparus rotundus [23]. Tsukamurellaceae monogeneric family is inclusive of the type species Tsukamurella paurometabola and the related species [24].

Frankiales: This order comprises families including Frankiaceae, Cryptosporangiaceae, Geodermatophilaceae, Acidothermaceae, Nakamurellaceae, and Sporichthyaceae [25-30]. Frankiaceae family is monogeneric and consists of type genus Frankia and type species Frankia alni [30]. Acidothermaceae family includes type genus Acidothermus and type species Acidothermus cellulolyticus) [29]. Cryptosporangiaceae family is related to genus Cryptosporangium and the type species Cryptosporangium arvum and three linked species Cryptosporangium aurantiacum, minutisporangium and japonicum [28]. Next family is Geodermatophilaceae and the monospecific genus is Geodermatophilus and the type species Geodermatophilus obscurus [25]. Other genera and species are type species Blastococcus aggregatus Saxobsidens and jejuensis and the type species Modestobacter multiseptatus and versicolor. Family Nakamurellaceae includes three monospecific genra Humicoccus ,Nakamurella, Saxeibacter [27]. Sporichthyaceae monogeneric family comprises of two species Sporichthya polymorpha and Sporichthya brevicatena [26].

Glycomycetales: Only family related to thic order is Glycomycetaceae which has three genra. Genus Glycomyces type species is Glycomyces harbinensis and it has nine other related species [31]. Next , genus Haloglycomyces , its type species is Haloglycomyces albus [32] and lastly Stackebrandtia contains the type species Stackebrandtia nassauensis and Stackebrandtia albiflava [31].

Jiangellales: The family Jiangellaceae and two genera are corrolated with the order. Genus Jiangella and its type scpecies Jiangella gansuensis and Jiangella alba and alkaliphila , Haloactinopolyspora genus and Haloactinopolyspora alba type species are arranged in this order [33].

Kineosporiales: The family Kineosporiaceae and the three genera inclusive of Kineosporia (type species Kineosporia aurantiaca and six related species) , Kineococcus (type species Kineococcus aurantiacus and four related species) and Quadrisphaera(type species Quadrisphaera granulorum) are in this order [34].

Micrococcales: This order encompasses following families: Family Micrococcaceae, Beutenbergiaceae, Bogoriellaceae, Brevibacteriaceae, Cellulomonadaceae, Dermabacteraceae, Dermacoccaceae, Dermatophilaceae, Intrasporangiaceae, Jonesiaceae, Microbacteriaceae, Promicromonosporaceae, Rarobacteraceae, Ruaniaceae, Sanguibacteraceae [35-41].

Micromonosporales: It is related to a single Micromonosporaceae family. The genra composed from this family are Actinocatenispora, Actinoplanes, Asanoa Micromonospora, Krasilnikovia, Catelliglobosispora and Hamadaea; Catellatospora, and Planosporangium; Couchioplanes, and Pseudosporangium; and Dactylosporangium and Virgisporangium [42,43].

Propionibacteriales: The linked families to this order are Propionibacteriaceae and Nocardioidaceae. Family Propionibacteriaceae contains of thirteen genera. This thirteen genre are classified into five clades [44]. Family Nocardioidaceae consists of the genera Actinopolymorpha, Kribbella, Nocardioides, Aeromicrobium, and Marmoricola [15,45].

Pseudonocardiales: The family Pseudonocardiaceae is grouped in two two clades. The first clade comprises the genra Kibdelosporangium, Pseudonocardia, Amycolatopsis, Actinomycetospora, Saccharomonospora, Prauserella, Saccharopolyspora, Sciscionella, and Thermocrispum. The second clade includes Lentzea, Actinosynnema, Saccharothrix, Lechevalieria, and Umezawaea. Arabinose and galactose exist in the first clade while mannose, galactose, and sometimes either rhamnose or ribose are found in the second clade [46].

Streptomycetales: Streptomycetaceae family is denoted to genera Kitasatospora Streptomyces and Streptoverticillium [45].

Streptosporangiales: The families Streptosporangiaceae, Nocardiopsaceae, Thermomonosporaceae are assigned for this order. Family Streptosporangiaceae is related to 11 genera. Family Nocardiopsaceae and family Thermomonosporaceae are similarly composed of 5 genra [47].

Class Acidimicrobiia

Order Acidimicrobiales: It involves two main families Acidimicrobiaceae and Iamiaceae. The family Acidimicrobiaceae consists of four monospecific genera including Acidimicrobium, Ferrimicrobium, Ferrithrix, and Ilumatobacter, The family Iamiaceae encompasss the monospecific genus Iamia [40].

Class Coriobacteriia

Coriobacteriales: This order contains the single Coriobacteriaceae family. The family encompasses six clades. One clade includes the monospecific genus Coriobacterium and Collinsella aerofaciens , intestinalis, and stercoris. Denitrobacterium detoxificans, Atopobium minutum,Adlercreutzia equolifaciens, Asaccharobactercelatus, and Enterorhabdus mucosicola, faecicanis, Cryptobacterium curtum, fossor, parvulum, Gordonibacter pamelaeae, rimae,and vaginae, and Olsenella uli and profusa, Eggerthella lenta and sinensis, and Paraeggerthella hongkongensis; and Slackia exigua , heliotrinireducens, and is oflavoniconvertens [48].

Nitriliruptoria: The order Nitriliruptorales and the family Nitriliruptoraceae are assigned for this class [49].

Class Rubrobacteria

4.6.1.Rubrobacterales: This order is mainly represented by the the family Rubrobacteraceae and the genus Rubrobacter [50].

Mechanisms of Actinobacteria Action

Actinobacteria are a group which are significant as producers of wide range of antibiotic products. Novobiocin, also termed as cathomycin or albamycin is produced by Streptomyces niveus. This compound is an aminocoumarin antibiotic.it targets GyrB subuni tof bacterial DNA gyrase which play a role in energy transduction [51]. Abyssomicin C is produced by marine Verrucosispora strain and strongly inhibits para-aminobenzoic acid.it acts potently against gram positive bacteria [52]. Bacteriocins are ribosomally manufactured and usually small peptides (<10 kDa) produced by bacteria in order to impede the growth of related bacteria species. This antimicrobial agents can also have a broad spectrum activity against non-related species [53]. Some can also reveal anti-allergic, antitumor, anti-inflammatory, antinociceptive activities and regulate bood pressure. Lanthipeptide are ribosomally synthesized peptides which undergo posttranslational alternation that induce rare amino acids production and display various bioactivities including antifungal, antimicrobial, and antiviral activities. Their modifications occur proceeding two main reactions: dehydration of threonine or serine residues on the way to form Dha or Dhb, and cyclization to form Lan or MeLan [54]. Lantibiotics are the term used for lanthepeptides exhibiting antimicrobial activity in which the cell wall synthesis is hindered by binding to lipid ll , hence the merge of precursurs with the cell wall and thus the cell membrane functions will be abberant [55,56].

Lantibiotics are devided into three subclasses based on their biosynthetic machinery [55]. Type one are modified by cyclase LanC and the dehydratase LanB, Type two are modified by bifunctional enzyme, LanM, with both activities and type three are modified by the type III is modified by a trifunctional enzyme, LanKC with kinase, lyse and cyclase activities. Microbisporicin A1 and A2 are classified in type one and produced by Microbispora corallina and Processed by LanB and LanC [57]. Variacin is type two , Processed by a bifunctional LanM and produced by Kocuria varians [58]. Labyrinthopeptins A1, A2 and A3 are type three , processed by LanKC and Actinomadura namibiensis [59]. Microbisporicin or NAI-107,a type one lanthibiotic, was chiefly observed in strains of Actinoallomurus spp [60]. And Microbispora corallina [61]. There are two main congeneres discovered named as microbisporicin A1 and A2. Both of them function as cell wall synthesis inhibitors and develop bacteriocidal effect. They bind to lipid ll and also to other bactoprenol-bound precursors and accordingly impairing cell membrane [62]. Microbisporicin/NAI-107 is a potent lantibiothic against both aerobic and anaerobic Gram-positive pathogens.

Planosporicin or lantibiotic 97518 ,type one lanthibiotic, is produced by Planomonospora sp. DSM 14920 and is a cell wall synthesis inhibitor likewise. Planosporicin and microbisporicin/ NAI-117 share mostly the same structure and mechanism of action [63]. Variacin is a type two lantibiotic, and was identified in two strains of Kocuria varians. Growth of an extensive range of Gram-positive food spoilage bacteria are hindered by variacin [58]. Michiganin A is known to be manufactured by Clavibacter michiganensis subsp. Michiganensis [64]. Holtsmark and al. suggested that the function of this compound is by inhibiting cell wall synthesis similar to the previous discussed compounds. It has a narrow spectrum of targets [65]. Actagardine is another type two lantibiotic which blocks the transglycosylation reaction and consequently inhibits the cell wall synthesis [66]. It shows a potent bioactivity against Gram-positive pathogens, specially Clostridium spp. And Streptococcus spp [67]. Lantibiotics belonging to the cinnamycin group are categorized as type two and known as Cinnamycin, duramycin and ancovenin. Cinnamycin is exclusively produced by Streptomyces spp while Duramycin is produced from Streptomyces cinnamoneus [68]. Cinnamycin inhibits anaerobic bacteria, Bacillus subtilis, yeasts and fungi And also impedes the proliferation of herpes simplex virus 1 [69]. Labyrinthopeptins, including LabA1, LabA2 and LabA3 , are type 3 lantibiotic and were observed in Actinomadura namibiensis DSM 6313 [70]. LabA1 exhibits antiviral activity against HIV and HSV, in which the cell entry of these viruses is impeded and cell-to-cell viral transmission of HIV is prevented [71]. NAI-112 is another type 3 lantibiotic is produced by Actinoplanes sp. DSM 24059 and act moderately against Staphylococcus spp. and Streptococcus spp with the mechanism explained above [72].

Pharmacological Properties of Actinobacters

Table 1: Anti-Microbial properties of Actinobacteria.

Actinobacter	Active Component	Bioactivity	Reference
A. baumannii	A mixture of iturin A2, iturin A3, and iturin A6 (Antifungal)	Inhibits the growth of Cryphonectria parasitica, Glomerella glycines, Phytophthora capsici, Fusarium graminearum, Botrytis cinerea, and Rhizoctonia solani	Hemala L, et al. [131]

Nocardiopsis prasina, Streptomyces violarus, Streptomyces krainskii, and Streptomyces tsusimaensis	-	Antimicrobial activity against Bacillus subtilis, methicillin resistant Staphylococcus aureus (MRSA), Escherichia coli ATCC 25922, Acinetobacter baumannii, Salmonella Typhi, and Candida albicans	Holtsmark I, et al. [64]
HAAG3-15 the most closely to Streptomyces sporoclivatus and S. antimycoticus	Azalomycin B	Showed antagonism against Fusarium oxysporum f. sp. cucumerinum, Corynespora cassiicola, Setosphaeriaturcica turcicaf, Colletotrichum orbiculare, Alternaria solani, Helminthosporium maydis, Sphacelotheca reiliana, Sclerotinia sclerotiorum, Phytophthora sojae, and Rhizoctonia solani	Holtsmark I, et al. [65]
Streptomyces capitiformicae 1H-SSA4, Streptomyces amphotericinicus 1H-SSA8 and Streptomyces lasiicapitis 3H-HV17, Streptomyces sp. 1H-GS5, and Streptomyces sp. 1H-XA2	A novel polyene amide compound and furamycins I and II	Rhizoctonia solani, Fusarium oxysporum, Curvularia lunata, Corynespora cassiicola, Setosphaeriaturcica turcicaf, Colletotrichum orbiculare, Alternaria solani, Helminthosporium maydis, Sphacelotheca reiliana, Sclerotinia sclerotiorum, Phytophthora sojae, Phytophthora capsici, and Phytophthora infestans	Hoyles L, et al. [20]
Streptomyces sporoclivatus, Streptomyces cavourensis, Streptomyces capitiformicae, and Streptomyces pratensis	azalomycins F4a, azalomycins F5a, bafilomycin B1, actinolactomycin, dimeric dinactin, tetranactin, dynactin, maremycin G, and a new maremycin analogue	Sclerotinia sclerotiorum	Hug JJ, et al. [74]
WA23-4-4 isolated from the intestinal tract of Periplaneta americanat considered as a novel Streptomyces	3-Acetyl benzoyl amide	Showed significant antifungal activity against Candida albicans ATCC 10231, Aspergillus niger ATCC 16404, Trichophyton rubrum ATCC 60836, and Aspergillus fumigatus ATCC 96918	Hui MLY, et al. [124]

Micromonospora auratinigra, a member of the family Micromonosporaceae, and Kocuria kristinae	Chloroanthraquinone, a novel bafilomycin analogue, and novel antimicrobial peptide	Showed inhibitory activity against Bacillus subtilis, Candida albicans, and Escherichia coli (Only the peptide from Kocuria kristinae)	Inderiati S [117]
Streptomyces, Nocardia, and Streptosporangium which ambiguously matched with Streptomyces niveus NRRL 2466 (T) and Streptomyces pulveraceus NBRC 3855 (T)	2,5-bis(1,1-dimethylethyl) phenol and benzeneacetic acid	Showed inhibitory activity against Staphylococcus aureus MTCC 96, Escherichia coli MTCC 40, Candida albicans MTCC 227, Staphylococcus aureus (MRSA) ATCC 43300, Staphylococcus saprophyticus, and Bacillus pumillus	Iorio M, et al. [61]
Most closely related to Pilimelia columellifera subsp. pallida GU269552(T)	Silver nanoparticles capped with proteins	Showed inhibitory activity against Malassezia furfur, Trichophyton rubrum, Candida albicans, and Candida tropicalis	Janardhan A, et al. [91]
VITGAP240 and VITGAP241 with predominant genus of Streptomyces	Type I polyketide synthases (PKS-I), PKS-II, and non-ribosomal peptide synthases (NRPS)	Showed inhibitory activity against Candida albicans	K Sharma, et al. [119]
Streptomyces sp. TD025 mostly closest to Streptomyces cirratus	Antimycin urauchimycins A and B	Showed inhibitory activity against Candida albicans	Kämpfer P, et al. [28]
Streptomyces albidoflavus NBRC13010 (AS25)	Non-polyenic lactone, antimycin A19	Showed inhibitory activity against resistant Candida tropicalis R2 and Pythium irregular (resistant to polyenes)	Kämpfer P [38]
Pseudomonas frederiksbergensis BZ21, Pseudomonas frederiksbergensis BZ27, Pseudomonas fluorescens BZ64, Serratia proteamaculans BZ56, and Serratia liquefaciens BZ65	Components in extraction were similar to Tetracycline and Rifampine (but further studies are needed) and serraticin A	Showed inhibitory activity against Escherichia coli, Shigella flexneri, Salmonella enterica, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, and Cryptococcus neoformans	Kämpfer P [132]

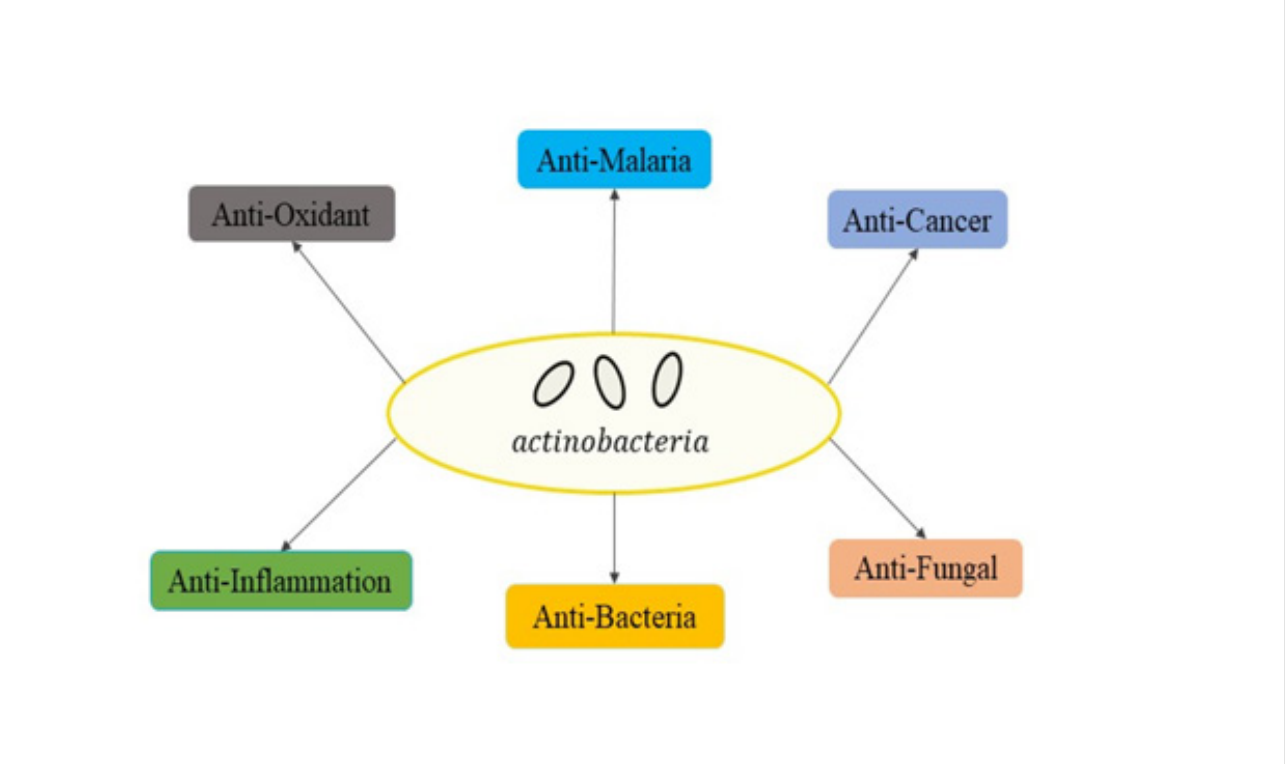

Figure 1: Actinobacteria properties.

Several studies different properties of Actinobacteria and shown their usage in various disorders. Here in we are going to represent their benefits in different situation as below (Table 1) (Figure 1).

Anti-Bacterial Effects: Bacterial pathogens can lead to deadly infectious diseases. Most bacterial infections are very difficult to treat due to antibiotic resistance obtained by pathogens [73]. Bacterial agents' resistance to a variety of antibiotics is spreading alarmingly around the world. New natural-derived antibiotics have also declined sharply in recent years. Due to the declining effectiveness of the drug on the market, researchers have begun to develop new alternatives for treating infections caused by pathogens. Thus, this has led to the discovery of strains of marine actinobacteria [74]. Hence, marine Streptomyces antibiotics have been used to prevent or treat diseases stimulated by microorganisms [75]. Continuous research is underway to develop an effective therapeutic drug by isolating biologically active molecules from rare actinobacterial bacteria [76].

Anti-Cancer Effects: Cancer is one of the most serious and deadly diseases. Current treatments including chemotherapy, immunotherapy, surgery and radiotherapy have not been very effective to date. Many antitumor compounds have been reported to be derived from Marine Streptomyces [77]. Marine actinobacteria are rich sources of antitumor compounds, for example, actinomycin, anthracycline, aureolic, mitomycin, bleomycin, pentostatin, resistomycin [78]. These factors are effective in the prevention and treatment of cancer with apoptosis, mitochondrial permeability, inhibition of signal transduction, morphological changes due to irregular cell differentiation, angiogenesis, DNA encoding and inhibition of RNA polymerase activity [79,80].

Anti-Inflammatory Effects: Inflammation occurs as an immune response to infection, irritation, or tissue damage. Various factors such as blunt trauma, foreign bodies, vibrations and chronic pressure are involved in causing inflammation [81]. Many natural products such as resveratrol, quercetin, curcumin, etc. have been used to revive the inflammatory process in various diseases [82-84]. Secondary bioactive metabolites from Streptomyces sp. It has been proven to have anti-inflammatory activity. Therefore, these compounds can be used as an up-to-date treatment method in the treatment of inflammatory diseases [85,86].

Anti-Malaria Effects: Malaria is caused by the protozoan, Plasmodium, which is parasitic in nature and accountable for more than 200 million reported clinical cases and over 3 million mortalities annually. P. falciparum, the causative agent, is becoming increasingly resistant to most of the drugs [87]. New therapeutic strategies are urgently required to battle this disease. Some of the compounds derived from the marine actinobacteria possess extremely high anti-plasmodial activity [88].

Anti-Viral Effects: Also, the antiviral properties of actinobacteria have been proven to play this role by various methods such as biological control of human anthropogenic virus contamination, control of disease transmission in wastewater and contaminated effects of chemotherapy for viral diseases [89]. These activities are mostly used in coastal areas, where water is needed for recreational activities or in the food industry, and directly affect the lifestyle and economy of the people [90].

Anti-Oxidative Effects: Antioxidants prevent deterioration, damage or destruction by the oxidation process. These bioactive compounds protect the body against oxidative stress by blocking or delaying oxidative damage caused by reactive oxygen species (ROS) [91]. Various mechanisms such as inhibiting the formation of free radicals, eliminating oxygen molecules and chelating metal prooxidants have been considered for them [92].

Human Fungal Diseases: Pathogenesis and Current Treatment: Challenges Facing Invasive fungal infections are a growing threat to human health. In the developed world, these infections are mainly occurring in the increasingly contextual [93]. Invasive immunosuppressive therapies are one of the treatments. Total mortality for invasive diseases caused by Candida species ([94]. And Aspergillus spp. 30-50%. Despite the emergence of new diagnostic and therapeutic strategies in the world, there are 1 million cases of Cryptococcus Which leads to the death of 675,000 people [95]. Due to the high degree of phylogenetic relationship between fungi and humans The development of therapeutic methods can be one of the main objectives of the study [96]. Fungi produce a large set of secondary enzymes and metabolites to fight and digest the outside world in order to fight for survival and with each other. Many antimicrobial agents are isolated from the fungi themselves. The best example is penicillin, which was isolated from Penicillium notatum (Penicillium chrysogenum) [97]. Most of studies concerning four human fungal pathogens that cause invasive infections including C. albicans, C. neoformans, A. fumigatus, and H.capsulatum. C. albicans is a commensal fungus which exists as a normal microflora in the human body but becomes pathogenic if the host immune defense system is weakened [98,99]. Currently, five classes of antifungal agents are used orally or intravenously to treat fungal infections in humans: polyenes, pyrimidine analogues, allylamines, azoles, and echinocandins [100].

Anti-Fungal Properties of Actinobacters; Novel Insight Against Fungi Pathogenesis: Lamari and al. exploited the new dithiolopyrrolone antibiotics , named as 3-methyl-2-butenoylpyrrothine, tigloylpyrrothine , and n-butyropyrrothine in addition to known iso-butyropyrrothine and thiolutine from an actinomycete strain , Saccharothrix sp. , which was extracted from saharian palm grove soil at Adrar, south Algeria [101]. These products revealed high antibacterial activity against Gram-positive bacteria Bacillus coagulans, Bacillus subtilis, and Micrococcus luteus except for Staphylococcus aureus. these compounds showed no or weak antibacterial activity against gram negative bacteria except Klebsiella pneumoniae that was highly inhibited [101]. Merrouche and al. in 2010 succeeded to extract the new dithiolopyrrolone derivatives valerylpyrrothine, isovalerylpyrrothine, formylpyrrothine and the known aureothricin. They showed moderate efficiency against some fungi Penicillium expansum, Mucor ramanniamus, and Aspergillus carbonarius [102]. Further ,Merrouche and al. in 2011 performed another study and the new dithiolopyrrolone (PR2, PR8, PR9 and PR10) were purified from the broth of Saccharothrix algeriensis. These four antibiotics were named as crotonyl-pyrrothine, sorbyl-pyrrothine, 2-hexonyl-pyrrothine and 2-methyl-3- pentenyl-pyrrothine , respectively. PR8 showed highest activity against gram negative bacteria compared to others. All compunds except PR10 was observed to have a moderate antibacterial activity against the tested fungi and yeasts. Moreover, PR10 demonstrated higher activity against Candida albicans and A. carbonarius.PR8 showed to be most active against gram positive bacteria [103]. Benzoyl-pyrrothine dithiolopyrrolone was obtained from Saccharothrix algeriensis NRRL B-24137, which showed high bioactivity against Listeria monocytogenes and acceptable MIC against several Gram-positive bacteria and filamentous fungi [104]. A new anthracycline antibiotic mutactimycin PR was discovered by a study conducted by Zituni and al., isolated from Saccharothrix sp. SA 103 strain and they also isolated the known mutactimycin C. These compounds revealed moderate bioactivity against some Gram-positive bacteria and fungi specifically Bacillus subtilis, Saccharomyces cerevisiae, and Mucor ramannianus [105].

Angucyclinone which is mostly isolated from the genus Streptomyces and also from Actinomadura, Nocardia and Streptosporangium genera is related to tetracyclines and anthracycline. It has broad spectrum and has a good efficacy against Micrococcus luteus ATCC 9314 and Bacillus subtilis ATCC 6633 [106]. Nonomuraea sp. NM94 strain secrets some antibiotics that some of them are shown to be active towards some Gram-positive bacteria, yeast, and fungi [107]. Saccharothrix species were the initial source of chloramphenicol production. Aouiche and al. indicated that Saccharothrix sp. PAL54A strain produces the known chloramphenicol [108]. Streptomyces sp. WR1L1S8 was utilized and its metabolites were isolated. The matabolites were the new polyketide known as 2-hydroxy-γ-pyrone tautomeric along with phaeochromicins B , C , and E. They showed inhibiting activity against the growth of both the Gram-positive and Gram-negative bacteria. Polyketide compound revealed a bacteriostatic activity against methicillin-resistant Staphylococcus aureus [109]. Actinomycete strain SA198 was isolated from a Saharan soil sample of Algeria by Boubetra and al. and Pure metabolites were extracted

which exhibited moderate activities against gram negative and gram positive bacteria and potent effects against phytopathogenic and toxinogenic fungi including Aspergillus carbonarius , Penicillium expansum , Mucor ramannianus [110]. Another study by Adel and al. isolated actinobacteria strain PAL114 from a Saharan soil in Algeria which produces antibacterial compunds. Two of these bioactive compounds are P44 and P40. The P40 is efficiently active against Candida albicans, Bacillus subtilis, and Staphylococcus aureus [111].

Chemically named, 2-amino-N-(2-amino-3-phenylpropanoyl)-N-hydroxy-3-phenylpropanamide, which was purified from Streptomyces WAB9 , revealed an appreciable antibiotic affect against some drug-resistant bacteria, filamentous fungi and yeasts. The effect was most notably against Pseudomonas aeruginosa IPA1 [112]. Isolation of di-(2-ethylhexyl) phthalate from the strain Streptomyces sp. G60 was reported by Driche, et al. [113]. This compound showed strong compound against different strains of Staphylococcus aureus and MRSA [113]. The actinobacterium strain ABH26 has shown that produces antimicrobial products. Two new cyanogriside antibiotics named cyanogriside I and cyanogriside J along with the three caerulomycins, caerulomycin F caerulomycin A and caerulomycinonitrile are produced by the strain. All the compounds had effect against the gram positive bacteria and caerulomycin F emerged the most bioactivity against gram postivie bacteria and also fungi [114]. Extensive research is underway to identify new antifungal compounds from actinobacteria that are effective against pathogenic fungi (Table 2). Among these bioactive compounds, we can mention scopafungin, candidi plancin, rapamycin, phthalates, etc., which have significant antifungal properties [115]. Metabolites derived from actinobacteria for applications such as cartilage tissue engineering, transport Drugs and nerve regeneration have been used. These antifungal metabolites include nystatin (Streptomyces noursei), amphotericin B (Streptomyces nodosus), and natamycin. (Streptomyces natalensis). Streptomyces sp. DA11 was found to be associated with Craniella sp. This species produced exonzyme chitinase which showed significant antifungal activity against Aspergillus sp and Candida sp [116]. kasugaensis is a bactericidal and fungicidal metabolite secreted by Streptomyces kasugaensis and acts as an inhibitor of protein biosynthesis in microorganisms ([117,118]. Isolated polyoxins B and D from the metabolites Streptomyces cacaoi var. asoensis. These substances interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of chitin [119]. The validamycin family was identified by researchers in the Takeda chemical industry in a greenhouse experiment for the treatment of pod blight in rice plants caused by Rhizoctonia solani. Validamycin A, the major and most active component of the complex, was isolated from Streptomyces hygroscopicus var. Limoneus [120]. Inside the fungal cell, validamycin is converted to credoxylamine A, a potent trehalose inhibitor that suppresses the breakdown of intracellular trehalose. Trehalase plays an essential role in glucose transport in insects and fungi. This procedure gives validamycin A a desirable biological choice because vertebrates do not depend on the hydrolysis of trehalose disaccharide for their [121].

Table 2: Anti-Fungal properties of Actinobacteria.

Actinobacter	Active Component	Antifungal Activity	Reference
A. baumannii	A mixture of iturin A2, iturin A3, and iturin A6 (Antifungal)	Inhibits the growth of Cryphonectria parasitica, Glomerella glycines, Phytophthora capsici, Fusarium graminearum, Botrytis cinerea, and Rhizoctonia solani	Hemala L, et al. [131]
Nocardiopsis prasina, Streptomyces violarus, Streptomyces krainskii, and Streptomyces tsusimaensis		Antifungal activity against Candida albicans	Holtsmark I, et al. [64]

HAAG3-15 the most closely to Streptomyces sporoclivatus and S. antimycoticus	Azalomycin B	Showed antagonism against Fusarium oxysporum f. sp. cucumerinum, Corynespora cassiicola, Setosphaeriaturcica turcicaf, Colletotrichum orbiculare, Alternaria solani, Helminthosporium maydis, Sphacelotheca reiliana, Sclerotinia sclerotiorum, and Rhizoctonia solani	Holtsmark I, et al. [65]
Streptomyces capitiformicae 1H-SSA4, Streptomyces amphotericinicus 1H-SSA8 and Streptomyces lasiicapitis 3H-HV17, Streptomyces sp. 1H-GS5, and Streptomyces sp. 1H-XA2	A novel polyene amide compound and furamycins I and II	Showed antagonism against Rhizoctonia solani, Fusarium oxysporum, Curvularia lunata, Corynespora cassiicola, Setosphaeriaturcica turcicaf, Colletotrichum orbiculare, Alternaria solani, Helminthosporium maydis, Sphacelotheca reiliana, and Sclerotinia sclerotiorum	Hoyles L, et al. [20]
Streptomyces sporoclivatus, Streptomyces cavourensis, Streptomyces capitiformicae, and Streptomyces pratensis	azalomycins F4a, azalomycins F5a, bafilomycin B1, actinolactomycin, dimeric dinactin, tetranactin, dynactin, maremycin G, and a new maremycin analogue	Sclerotinia sclerotiorum	Hug JJ, et al. [74]
WA23-4-4 isolated from the intestinal tract of Periplaneta americanat considered as a novel Streptomyces	3-Acetyl benzoyl amide	Showed significant antifungal activity against Candida albicans ATCC 10231, Aspergillus niger ATCC 16404, Trichophyton rubrum ATCC 60836, and Aspergillus fumigatus ATCC 96918	Hui MLY, et al. [124]
Micromonospora auratinigra, a member of the family Micromonosporaceae, and Kocuria kristinae	Chloroanthraquinone, a novel bafilomycin analogue, and novel antimicrobial peptide	Showed inhibitory activity against Candida albicans	Inderiati S [117]

Streptomyces, Nocardia, and Streptosporangium which ambiguously matched with Streptomyces niveus NRRL 2466 (T) and Streptomyces pulveraceus NBRC 3855 (T)	2,5-bis(1,1-dimethylethyl) phenol and benzeneacetic acid	Showed inhibitory activity against Candida albicans MTCC 227	Hug JJ, et al. [74]
Most closely related to Pilimelia columellifera subsp. pallida GU269552(T)	Silver nanoparticles capped with proteins	Showed inhibitory activity against Malassezia furfur, Trichophyton rubrum, Candida albicans, and Candida tropicalis	Hui MLY, et al. [124]
VITGAP240 and VITGAP241 with predominant genus of Streptomyces	Type I polyketide synthases (PKS-I), PKS-II, and non-ribosomal peptide synthases (NRPS)	Showed inhibitory activity against Candida albicans	Iorio M, et al. [61]
Streptomyces sp. TD025 mostly closest to Streptomyces cirratus	Antimycin urauchimycins A and B	Showed inhibitory activity against Candida albicans	Janardhan A, et al. [91]
Streptomyces albidoflavus NBRC13010 (AS25)	Non-polyenic lactone, antimycin A19	Showed inhibitory activity against resistant Candida tropicalis R2	K Sharma, et al. [119]
Pseudomonas frederiksbergensis BZ21, Pseudomonas frederiksbergensis BZ27, and Pseudomonas fluorescens BZ64	serraticin A	Showed inhibitory activity against Candida albicans and Cryptococcus neoformans	Kämpfer P, et al. [28]

Conclusion

The growing need for drug discovery has led to new technologies in clinical trials. Intensive research is being developed into the discovery and synthesis of less complication and more effective antifungal drugs [122]. Due to the various applications of natural compounds in medicine, food and health in the last six decades, more than ten thousand natural compounds have been derived from various microbial sources. Actinomycetes are most commonly distributed in environments such as terrestrial, marine, or extreme conditions. Streptomyces is the largest genus of Actinobacteria in the family Streptomycetaceae [123]. These are gram-positive bacteria with high GC content that perform various functions such as antibacterial, anti-fouling, anti-fungal, anti-inflammatory, anti-parasitic, anti-tumor, anti-viral, insecticidal, growth-promoting metabolites and enzyme inhibitors [124]. This is one of the important reasons why this group of organisms has been widely considered in the treatment of various diseases [125]. In this study, actinobacteria are described and introduced as a new antifungal agent that can be widely used in the prevention and treatment of fungal diseases [126-141].

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