Review Article

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Application of actinomycetes in the control of *Salmonella species*

Abstract

This review is purposed to highlight the potential of finding novel antibiotics by screening various metabolites of actinomycetes. A significant global issue is drug-resistant bacteria and fungi that cause infectious illnesses. The emergence of multi-drug resistant *Salmonella* species have caused immense public health concern due to the resulting negative impacts. *Salmonella* causes foodborne illnesses, which result in significant monetary loss and a high death rate. The majority of *Salmonella* species are zoonotic infections, meaning they can spread from animals to people when they consume tainted meat, animal products, or other food items that have been contaminated with excrement from other animals. The overuse of antibiotics in treating *Salmonella* infections has increased the urgency to search for new potential sources of effective antibiotics. Actinomycetes are a group of bacteria species found in soil that create vital biological products, primarily powerful antibiotics. actinomycetes make up about two-thirds of all antibiotics, with Streptomyces species producing the majority of them. Several studies have shown that there is an abundant of potent antibiotics produced by actinomycetes. These bioactive compounds have been extensively demonstrated to cause bactericidal and bacteriostatic activities. Thus, more intensity should be put into unraveling more potential antibiotics from actinomycetes to help reduce the burden of drug resistance.

Keywords: actinomycetes, drug-resistant, antibiotics, *Salmonella*

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Introduction

Actinomycetes are a group of bacteria species found in soil that create vital biological products, including powerful antibiotics. Actinomycetes are actually the primary source from which the majority of antibiotics are created.[1] Antibiotics are typically low-molecular-weight compounds that are able to prevent or limit the growth of harmful bacteria. Antibiotics are secondary metabolites and do not contribute to the growth and development of the organism.[2–4]

During the late log phase of growth and up to their stationary phase, actinomycetes naturally create antibiotics. One of their main advantages is the ability to suppress the growth of other microorganisms thriving in the same habitat in nature. In addition to antibiotic production, actinomycetes, coexist with other species and endure for a very long time in the natural world.[5–9]

They were once thought to be an intermediary between fungi and bacteria. Actinomycetes have a cell wall structure that is similar to that of gram-positive bacteria. Additionally, they are branching unicellular microbes. When grown on a substrate, actinomycetes produce mycelium.[10] In some species, the mycelia can split into rod- or coccoid-shaped. Many genera also produce spores, which can be detected as sporangia or spore cases on aerial hyphae, on the surface of the colony, or floating freely in the environment. They have DNA that has a high guanine and cytosine content (>55%). *Streptomyces* are the most prevalent microbe in these categories. The others are referred to as rare actinomycetes or non-actinomycetes. Most actinomycetes are free-living organisms.[1,2,5,11]

Due to their intricate metabolic processes, actinomycetes are known to create a variety of metabolites. Beta-lactam antibiotics like penicillin and cephalosporins, as well as various forms of shikimic acid, such as chloramphenicol, are among the over 23,000 known secondary metabolites produced by microorganisms.[5]

Actinomycetes are known to create 42% of these compounds, followed by fungi and other bacteria with 16% each. Streptomyces, Saccharopolyspora, Amycolatopsis, Micromonospora, and Actinoplanes are the principal producers of commercially significant biomolecules among numerous species. The environment receives these metabolites.[12–15]

The primary impact of those who produce antifungal and antibacterial metabolites on their immediate environment is the prevention of other microbes from proliferating or developing. The biological antagonistic types relate to these classes of actinomycetes. Since these are utilized and their metabolites are used to make antibiotics, they are of particular importance.[10,16,17]

A significant global issue is drug-resistant bacteria and fungi that cause infectious illnesses.[18–20] To tackle them, new antimicrobial agents must be developed. Actinomycetes are a significant source of bioactive compounds with significant medical and commercial value, especially in the field of biotechnology.[20–23] According to Takizawa *et al.*[24] actinomycetes make up about two-thirds of all antibiotics, with Streptomyces species producing the majority of them. This bacterial group is intriguing since it has a complicated life cycle and a variety of species that produce antibiotics.[2,13,25]

Among the most common harmful bacteria that infect both humans and animals are the *Salmonella* species. When treating *salmonella* infections, the use of antibiotics has proven to be lifesaving.[10,18,27] Worldwide, *Salmonella* spp. is responsible for human infections and financial losses.[9] *Salmonella* spp. can flourish in a variety of meals, including poultry, pork, vegetables, and other foods. *Salmonella* spp. are commonly found in chicken products, which are also a significant source of this infection in both humans and animals.[17,18,21] *Salmonella* causes foodborne illnesses, which result in significant monetary loss and a high death rate. The majority of *Salmonella* outbreaks in the past ten years were linked to reservoirs in poultry.[9,28] Finding new, powerful alternatives for the prevention and treatment of *Salmonella* infections is therefore crucial. Currently, there are a number of effective antibiotics that are applied for the treatment and control of *Salmonella* infections and growth such as quinolones, sulfonamides, and aminoglycosides, etc. However, the number of effective antibiotics against the activities of *Salmonella* species is diminishing. Thus, it is imminent to explore effective alternatives to the fading antibiotics. This review is aimed at assessing the potential of actinomycetes as a source of antibiotics for the control of *Salmonella* species.

Salmonella spp

Salmonella is a gram-negative, motile, non-spore-forming, rod-shaped facultative anaerobic bacteria that belong to the *Enterobacteriaceae* family.[15,29] *Salmonella* species *enterica* and *bongori* are further classified into six subspecies based on the taxonomy created by Le Minor and Popoff in 1987.[27,15] Because it was formerly believed that each serotype had its own species, the genus *Salmonella* was previously divided into a number of other species.[30,31] With the development of more sophisticated genetic methods like DNA sequencing and hybridization, it was shown that many of the serotypes shared a significant degree of genetic similarity.[6]

Sources of Salmonella

The majority of *Salmonella* species are zoonotic infections, meaning they can spread from animals to people when they consume tainted meat, animal products, or other food items that have been contaminated with excrement from other animals.[19] Contamination of food and water initiates pathogenesis.[17] *Salmonella* spreads by direct or indirect contact with animals that have the infection, as well as the intake of tainted water or food. Animals such as mammals, birds, reptiles, amphibians, fish, shellfish, and even insects could harbor *Salmonella* in their intestines.[19,20] *Salmonella* does not typically come from natural water. Therefore, if they are discovered in water, it means that the water has been contaminated by feces. One of the most important medium used in the detection of *Salmonella* species is the *salmonella*-Shigella agar.[20] The identification of *Salmonella* species is usually done by testing the organisms' ability to produce hydrogen sulfide, ferment glucose, and its inability to ferment lactose. However, growth on *Salmonella*-Shigella agar, which is a selective and differential medium makes it possible for researchers to easily identify *Salmonella* species with the production of black pigments which indicates hydrogen sulfide production.[19]

The primary cause of food and water contamination, which significantly contributes to *Salmonella*'s spread across the environment and into the food supply, is fecal contamination.[19] *Salmonella* is stored in meat animals.[19] *Salmonella* is transmitted to chickens both vertically (through their parents) and horizontally (via feed, insects, rodents, people, transportation, and environmental facilities). However, horizontal transmission is a significant issue for *Salmonella* infection in hens.[9]

Pathogenesis of Salmonella in humans

In humans, salmonellosis can lead to four different types of illness: enteric fever, gastroenteritis, bacteremia, and other illnesses that aren't related to typhoidal salmonellosis.[3,17]

Enteric fever

Typhoid fever is brought on by *Salmonella* typhi, whereas paratyphoid fever is brought on by *Salmonella paratyphi* A, B, and C.[3,17] *Salmonella enterica* serovars paratyphi and typhi are the particular pathogens that cause enteric fevers in humans.[9]

Gastroenteritis

At least 150 *Salmonella* serotypes, including S. Typhimurium and S. enteritidis, are responsible for non-typhoidal salmonellosis or enterocolitis. Instead of human waste, infection always happens when someone consumes contaminated food or water.[3,17] Farm animals are the reservoirs for nontyphoidal *salmonellae* such as *Salmonella* enterica, and they are not human-restricted. Non-thyphoidal *Salmonella* species do not cause typhoid fever in humans.[9]

Bacteremia and other complications of nontyphoidal salmonellosis

Bacteremia develops in about 8% of untreated salmonellosis cases. Bacteria entering the circulation after crossing the intestinal barrier cause the dangerous illness known as bacteremia. In cases of fever of unknown etiology, *Salmonella*-caused bacteremia should be considered.[3,17]

Chronic carrier state

Salmonellosis can spread through chronic carriers, who may infect a large number of people, especially those who work in the food industry. Depending on the serotype, nontyphoidal serotypes typically survive in the digestive system for 6 weeks to 3 months.[17]

Drug resistance in Salmonella

Salmonella multi-drug resistance (MDR) is defined as resistance to the conventional first-line antibiotics chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole.[17] In a recent systematic review, reports from 38 countries on the detection of antimicrobial resistance of *Salmonella* were done. Over 55,459 isolates were tested for their resistance profiles. These studies used both the disk diffusion and micro-broth dilution method of antimicrobial sensitivity testing.[17] A total of 34,996 *Salmonella* Typhi isolates had resistance to ampicillin (31.8%), trimethoprim-sulfamethoxazole (37.3%), and chloramphenicol (25.9%) among them. 12,666 (35.5%) of the 35,659 isolates were MDR, 9,495 (64.7%) of the 14,671 isolates were resistant to nalidixic acid, and 5,406 (15.0%) and 6,979 (19.4%) of the 35,975 isolates were resistant to ciprofloxacin and intermediate, respectively. Of the isolates, 270 (4.5%) of 6,043 and 450 (1.3%) of 35,302 were resistant to azithromycin and ceftriaxone, respectively.

In another study, Adamu *et al.*,[3] found that the majority of *Salmonella* isolates from hospitalized patients were susceptible to first-line medications, such as macrolides and cephalosporins, using the disk-diffusion test. On the other hand, a significant percentage of isolates—93.3%—were resistant to quinolones (including 26 Paratyphiserovar and 58 Typhian) although only about 14% were resistant to fluoroquinolones. Higher sensitivity and specificity were attained when the MIC breakpoints were modified as follows: 4 µg/ml for azithromycin, ≥1 µg/ml for ciprofloxacin, 2 µg/ml for ofloxacin, 8 µg/ml for nalidixic acid, and 1 µg/ml for cefixime.

Antibiotic resistance manifested by a species of bacteria to at least three different antibiotic classes is known as multi-drug resistance (MDR).[22] The majority of multidrug-resistant *Salmonella* infections are contracted by the ingestion of tainted items derived from animals, such as swine and chicken eggs. This raises serious concerns about multidrug resistance.[17]

Over 47 million new cases of domestically acquired foodborne disease occur each year in the United States, and at least 70% of the pathogenic organisms implicated are resistant to a minimum of one antimicrobial medication, according to the Centers for Disease

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Control (CDC).[6] Every year, chronic disorders claim the lives of about 3,000 patients in the US. The CDC website states that drug-resistant infections result in a longer stay in the hospital and more expensive treatments, some of which may even be harmful to the patient. The issue seems to be getting worse rather than better as more germs develop multidrug resistance.[19] Chicken is the primary source of non-typhoidal *Salmonella* and is associated with antibiotic resistance. *Salmonella* spreads via the food chain, such as poultry production, and has multiple medication resistance profiles.[14]

Actinomycetes

The gram-positive, aerobic Actinomycetes are members of the Actinomycetales order and exhibit both substrate and aerial mycelium growth during their entire life cycle. Out of the 18 primary lineages that have so far been identified as existing inside the bacterial domain, this constitutes one of the major taxonomic groups.[13] Some actinomycete genera, including; *Actinoplanes, Catenuloplanes, Amycolatopsis, Micromonospora, Kineospora, Dactylosporangium, Microbispora,* and *Nonomuraea,* are referred to as "rare actinomycetes" since they can be difficult to isolate and culture because of their slow growth.[18,22] Actinomycetes are potential manufacturers of medicinal chemicals, antibiotics, and bioactive substances found in secondary metabolites. These consist of enzymes, immunosuppressive substances, anticancer substances, and antibiotics. In laboratory settings, actinomycetes are usually grown on Actinomycetes medium. This medium has been severely reported to have a high performance in the cultivation of actinomycetes species.[14,18] However, some of the species of actinomycetes are slow growers. Most researchers have recommended incubating the species on Actinomycetes medium for longer durations.[18]

Actinomycetes exhibit a variety of life cycles that are unique to prokaryotes and become important players in the cycling of organic materials in soil environments.[32] Researchers have shown that actinomycetes make a lot of bioactive secondary metabolites. Based on this, finding new antibiotic and non-antibiotic guide molecules by screening microbial secondary metabolites is becoming more and more important.[14] Actinomycetes (Actinobacteria) are also crucial for agriculture, human medicine, and food production. Their ability to collaborate with other creatures is the main driver behind this activity.

Ecology and habitat of actinomycetes

The most prevalent microorganisms, actinomycetes, have a hyphae-like appearance under cultivation and are the cause of the characteristically "earthy" odour of recently dug well dirt. In nature, actinomycetes emerge as thread-like filament structures.[7] Actinomycetes are a widespread collection of microorganisms that are widely disseminated in typical ecosystems, roughly all over the world. They have a diversity of environmental habitation patterns.[20] They mostly live on the soil, but they have also been widely dispersed in a variety of aquatic biological units, including sediments from marine settings.[11]

Additionally, it has been confirmed that they may survive under harsh environmental circumstances, particularly in cryophilic locations.[31] Actinomycetes are the most numerous occupants in soil sources, according to a proportionate survey, and they produce a surface layer that gradually disappears as depth increases. At all soil levels, actinomycete strain characteristics can be identified.[8]

Actinomycetes are frequently heterotrophic in their surroundings as well. While some of them come via parasitic or mutualistic relationships with other plants and animals, the majority of these are strict saprophytes. Actinomycetes, some of which are anaerobic like actinomycetes, are usually thought to play a part in the recycling of nutrients.[11] Many actinomycetes are growing on the common bacteriological media used in the laboratory, such as nutrition agar, blood agar, trypticase agar, starch casein agar, and brain heart infusion agar. However, other species, such as Frankia, require extremely specific growth media and incubation conditions. For the enhancement of spore characteristics and pigment formation in sporo-actinomycetes, however, particularly special media are required.[16]

Antibiotic production by actinomycetes in the Soil

Although antibiotics have never been found in natural soil, research has been done to look at the development of secondary metabolites in unamended and modified sterile soil microcosms that have been inoculated with the microbes that produce them. One of the clearest examples demonstrated how *Streptomyces venezuelae* created chloramphenicol when the bacterium grew in sterilized soil.[22] The amount of nutrients incorporated into sterile soil microcosms and the amount of antibiotic synthesis by a bacterial inoculant were shown to be directly correlated.[11]

In one study, Chavan *et al.*,[33] recovered thirty actinomycete colonies in pure culture from five soil samples using a starch-casein-nitrate-agar medium. Based on the color of their aerial mycelia, the isolates were sorted into five color groups and tested for antimicrobial activity against a variety of test microorganisms. The moderate to high activity of sixteen isolates (53.3%) against four gram-positive and four gram-negative bacteria was discovered.

In a similar study using the micro-dilution method, the antibacterial activity of fifty-four actinomycetes against fifteen test species, including three phytopathogens, was isolated and examined. Three particular strains among these nine isolates were discovered to possess noticeably higher levels of antibacterial potential and to be effective throughout a wider spectrum. With an IC50 value of 0.242 ± 0.33 mg ml−1 and antibacterial activity with a MIC value of 0.05 mg ml−1, the most effective actinomycetes were demonstrated.[16]

Conclusion

With the ever-increasing number of antimicrobial-resistant microorganisms, the application of actinomycetes to control the growth of pathogens is key to winning the arms race against superbugs. *Salmonella* species are well known for contaminating food sources, especially in developing countries where safety practices and regulations are not strictly adhered to. Frequent and indiscriminate use of antibiotics to treat *Salmonella* infections has resulted in their resistance to commonly used antibiotics. Actinomycetes offer us hope and high potential for solving this pressing challenge.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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