Biotechnological Journal of Environmental Microorganisms (BJEM)

Biotechnological Journal of Environmental Microorganisms(BJEM) 1(3) 2022 165-176

Microbial Secondary Metabolites to Control Disease: A Mini-Review

Bahareh Nowruzi*, Negin Khoshnood, Sara Sory, Sogol Gharooni Fard, Mohammad Reza Rezaei, Fatemehsadat Ayoub Nejad, Neda Farhoudi Fard

Department of Biotechnology, Faculty of Converging Sciences and Technologies, Science and Research Branch, Islamic Azad University, Tehran, Iran

Received: 26 August 2023/ Revised: 13 September 2023 /Accepted: 13 September 2023

Abstract

Bacterial infections are a significant hazard to public health worldwide, and because of their significant negative effects on public health, they are given high attention in national health programs in many nations. Over the past few decades, bacterial drug resistance has increased, while the rate of new antibiotic discoveries has consistently declined. Due to technological and financial advantages, the search for new, effective antibacterial agents has become a top priority. As a result, alternative medicines and new methods for the manufacturing of microbial products have been developed. An unparalleled genetic potential has been established for the creation of secondary metabolites by various microorganisms in the environment and microbiota, thanks to the work of gene editing and next-generation sequencing. Secondary metabolites serve crucial roles in cell development, signal transduction, nutrition seeking, communication, intra- and interspecies competition, and the production of organic compounds with low molecular mass. Therefore, the potential use of secondary metabolites in place of conventional antibiotics has drawn increased interest from researchers. Treatment must switch to second- or third-generation antibiotics as soon as bacteria become resistant to first-generation antibiotics. The need to find novel, powerful small compounds with high anticancer potential and a benign safety profile is real; however, the majority of anticancer medications used today have side effects. The goal of this review is to evaluate the potential uses of various types of microbial secondary metabolites for the prevention and treatment of infectious illnesses, as well as their costs, advantages, drawbacks, and side effects.

Key words: Advantages, Control Disease, Costs, Microbial Secondary Metabolites, Side Effects

* Corresponding author: bahareh.nowruzi@srbiau.ac.ir

1. Introduction

One of the biggest threats to global public health is communicable illness. In reality, many diseases traverse international borders at an unprecedented pace as a result of the globalization of commerce and travel, increasing the exposure and interdependence of individuals all over the world (Burci et al., 2018).

Due to their serious effects on public health, communicable diseases—which are illnesses brought on by viruses or bacteria and spread by contact with contaminated surfaces, bodily fluids, blood products, insect bites, or the air—have been given top priority in national health programs around the world. There are several examples of communicable illnesses, some of which need to be reported to the relevant government agencies or health departments in the area of the epidemic (Edemekong & Huang, 2017; HabibiSaravi et al., 2019). In all parts of the world, infectious illnesses brought on by bacteria constitute a significant source of mortality and morbidity. The bulk of therapy at the moment is supportive and conservative management. Personal cleanliness and vaccination, whether active or passive, are both forms of prevention. Over the past few decades, bacterial drug resistance has increased, while the rate of new antibiotic discoveries has consistently declined. Therefore, it has become of utmost importance to find novel potent antibacterial agents (Edemekong et al., 2017; Gorlenko et al., 2020). Primary metabolites are produced in part by the bacterial metagenome, which also converts tiny protein molecules into secondary metabolites (sometimes known as "specialized metabolites"). They are of considerable interest to researchers who are exploring them as potential substitutes for conventional antibiotics since they play a significant role in cell development, signal transmission, the hunt for resources, intra- and interspecies communication, and competition (Andryukov et al., 2019).

After the development period, microorganisms produce complex biological molecules known as microbial secondary metabolites (SMs). SMs are crucial for various secondary demands but play no part in the development and reproduction of the microorganisms themselves. These substances have uses in cosmetics, food, medicines, and other industries (Kumar et al., 2021). The most well-known examples of SMs are pharmacological drugs with a lengthy history and a high rate of success, such as penicillin, tetracyclines, and gentamicin sulfate. With their use as herbicides, insecticides, plant growth regulators, and other goods like bio-pigments and surfactants, SMs have recently found use in agriculture areas as well (Kumar et al., 2021).

Low-molecular-mass products are secondary metabolites produced by microbes. They are typically created during the generating microorganisms' late development phase and have peculiar shapes. The kind and quantity of nutrients used to make the culture medium can have a big impact on how it is synthesized (Ruiz et al., 2010). Microorganisms are crucial to the ecosystem and necessary for all living forms. They are the main source of nutrients and the world's principal recycler. From the abyssal zone to the stratosphere (at altitudes up to 60 km), microorganisms may be found and flourish in a very broad range of environmental conditions, from arctic cold to scorching volcanoes. These tiny creatures serve as a source of food and feed supplements, as well as being utilized to prepare a range of dishes (Demain, 2014).

Due to technological and financial benefits, new technologies for the manufacture of microbial products are replacing synthetic manufacturing methods. These goods include pharmaceuticals, organic acids, agriculturally significant metabolites, enzymes, flavoring compounds, and nutritional supplements, including vitamins and amino acids.

Amino acids, nucleotides, and fermentation byproducts like ethanol and organic acids are examples of primary metabolites. These compounds are thought to be necessary for the development of microbes. Due to its simplicity in producing enantiomerically pure amino acids at a low cost and ecological acceptability, microbial synthesis is emerging as the predominant and ideal method for amino acid manufacturing. Organic substances known as secondary metabolites are those that occur at or at the end of the stationary phase of growth and are not directly linked to the expan-

sion, maturation, or reproduction of microorganisms. These products have a significant role in healthcare as antibacterial, antiparasitic, anticancer, enzyme inhibitors, immunosuppressive, etc. drugs (Singh et al., 2017).

Diabetes, obesity, cancer, metabolic brain diseases, and other metabolic disorders, together with infectious diseases brought on by bacteria, fungi, and viruses, make up a large fraction of the illnesses and disorders that plague the world's population of people. These illnesses and disorders are caused by oxidative stress and inflammation, which are also prognostic indicators and visible symptoms of these conditions. The possibility of concurrent metabolic problems is very high. Interestingly, in the case of viral disorders, natural sources have strongly and significantly contributed to the production of the medications, either directly or by their derivation. Most antibiotics used to treat bacterial and fungal illnesses are either natural or developed from them. We have attempted to conceal information on the secondary metabolites that are useful in treating certain illnesses and disorders in the current special issue (Singla, 2020).

Numerous forms of metabolic illnesses and disorders, including but not limited to diabetes mellitus, cardiovascular problems, obesity, and cancer, are brought on by an unhealthy and sedentary lifestyle, heredity, and environmental factors (Shen & Singla, 2020). A great source of novel bioactive chemical entities for drug development is microbial natural products. A novel genetic potential for the creation of secondary metabolites by a variety of microorganisms prevalent in the environment and the microbiota has been discovered through attempts to alter genes and next-generation sequencing (Baral et al., 2018).

An illness that may be spread from one person to another by direct contact, indirect contact with an intermediary host, or indirect contact with a vector is known as a communicable disease. The term "communicable diseases" refers to a group of illnesses that extend beyond the spread of infectious diseases from one person to another. These illnesses include parasitic conditions, infections spread by insects or other animals, diseases that may be contracted from contact with 200 different types of noses, and all other diseases that are transmissible. Both epidemic and endemic forms of communicable illnesses exist. A novel infection or the development of a disease that lasts longer than expected constitutes an epidemic (Webber, 2019).

In this reviwe, we have provided detailed information on the types of microbial secondary metabolites for the control of infectious diseases by examining the cost, benefits and side effects.

2. Secondary Metabolites to Control Diseases

The organic substances that are created by an organism as part of its metabolic processes are known as secondary metabolites. They have been correctly referred to by a few researchers as auxiliary chemicals or specialized metabolites. They stand for a category of structurally varied and complex bioactive chemicals with low molecular weights that inhabit an uncommon chemical property region. They are created by bacteria during their late development phase, and their synthesis is often suppressed during logarithmic and stationary growth stages. These are generated to provide a particular advantage to the organism but are not necessary for its development or reproduction. Secondary metabolites are necessary for an organism to communicate with other living things, deal with stress, get nutrition, and engage in competition with commensals. Particularly prolific in producing antibiotics, microbes have been shown to be a rich source of SMs that have effectively been developed as essential therapeutic leads. Using the scaling law and lognormal model of biodiversity, Locey and Lennon recently assessed the biodiversity of microorganisms. According to their estimates, 1 trillion different types of microorganisms live on Earth. In this vast pool of microorganisms, certain bacteria could be able to create tiny compounds with important medicinal qualities. Human health has greatly benefited from the work of the bacterial kingdom, which is also acting as a repository for beneficial secondary metabolites (Baral et al., 2018; Mohan et al., 2022).

Actinobacteria is the genus that has given rise to more than 5000 antibiotics, whereas Mycobacteria has given rise to 500 natural goods. *Streptomyces* bacteria that live in soil

are especially skilled makers, with 7600 SMs discovered up to 2005. Computational predictions suggest that these bacteria may be able to manufacture 150,000 different antimicrobial agents. In addition to conventional antibiotics, microbial cultures have served as a source for immune-suppressants, antibiotics, anti-proliferative, cytotoxic, anti-hypertensive, and antiviral substances (Baral et al., 2018).

Bacillus species generate an estimated 795 secondary metabolite antibiotics. This species also produces a wide range of additional secondary metabolites, with *B. subtilis* and *B. amyloliquefaciens* accounting for a sizable portion of the documented *Bacillus* lipopeptide and polyketide diversity. Polyketide and lipopeptide synthesis in species found in other settings (such as water) is either very low or nonexistent, which highlights the significant function that these secondary metabolites serve in habitats associated with plants. Actinomycetes may thus be thought of as a source of secondary metabolites. Furthermore, only 1% of actinomycetes have been grown so far, necessitating the necessity for bioprospecting actinomycetes as well as other bacterial species from uncharted environments for the discovery of physiologically active compounds. Only a tiny number of these bacteria's small molecules have been carefully examined for their pharmacological properties, despite the large number of small molecules that have been isolated from them (Horak et al., 2019).

Over 160 antibiotics are available. Some of these are *Streptomyces* griseus, which has 40 antibiotics, and *Streptomyces hygroscopicus*, which has over 200 antibiotics. The most widely used broad-spectrum antibiotics, tetracyclines, play a significant role in treating illnesses brought on by a variety of microorganisms, including chlamydiae, rickettsiae, gram-positive and gram-negative bacteria, protozoan parasites, and mycoplasma. Another broad-spectrum antibiotic, ciprofloxacin, is efficient in treating gonorrhea, skin and bone infections, chancroid, and urinary tract infections (Singh et al., 2017).

Pharmaceutical products, particularly anti-infective derivatives, account for 62% of the antibiotic market. These include *Bacillus subti*lis, which has over 60 different compounds, as well as sera, immunoglobulins, vaccines, 12% anti-HIV antivirals, 7% antifungals, and 6% non-HIV antivirals. As said, more than 60% of anticancer formulations contain natural products and their derivatives. Actinomycin D, bleomycin, mitosanes (mitomycin C), anthracenones (mithramycin, streptozotocin, and pentostatin), enediynes (calicheamicin), taxol, and epothilones are some of the antineoplastic molecules derived from actinobacteria that are currently being used. The plant *Taxus brevifolia,* the endophytic fungus Taxomyces andreanae, and *Nodulisporium sylviforme* are the sources of the nonactinobacterial chemical known as taxol. It prevents the disintegration of microtubules, which is a crucial process in cell division, and slows the development of rapidly dividing cancer cells. It works well against breast cancer and advanced Kaposi's sarcoma. Additionally, *Pythium*, *Phytophthora*, and *Aphanomyces* are reported to be resistant to its antifungal effects.

There are several fungus-based statins that decrease cholesterol, including compactin, lovastatin, and pravastatin. A. terreus makes the drug lovastatin. The immunosuppressants, including cyclosporin A, tacrolimus, sirolimus (rapamycin), and mycophenolate mofetil, are of major significance in human medicine. They were crucial in the development of the area of organ transplantation and are used for heart, liver, and kidney transplants. The fungus *Tolypocladium niveum* produces the antibiotic cyclosporin A. The earliest known antibiotics, mycophenolic acid and mycophenolate mofetil, are both semi-synthetic derivatives produced by the same fungus. The *Streptomycete* produces the antibiotics tacrolimus and sirolimus.

Probiotic bacteria's metabolic products are thought to be effective in treating and preventing obesity, lowering weight gain, extending feelings of satiety, decreasing food intake, reducing fat deposition, boosting energy metabolism, and treating and strengthening insulin sensitivity. In a healthy human gastrointestinal tract, firmicutes and bacteroidetes predominate. Patients with irritable bowel syndrome who experience constipation more often were shown to have low-

er concentrations of bacteroidetes. Microbially produced carotenoids are utilized as food coloring, in fish feed, in nutraceuticals, in cosmetics, and as antioxidants. Carotene, which is obtained from *Blakeslea trispora, Dunaliella salina*, and lycopene, which is derived from *Blakeslea trispora* and *Streptomyces chrestomyceticus*, subsp. rubescens, is a frequently used food colorant. Fish feed is permitted to contain astaxanthin made from *Xanthophyllomyces dendrorhous*. Due to its superior antioxidant properties, zeaxanthin, canthaxanthin, lutein, and alpha-carotene are employed as nutraceuticals. The microalgae *Schizochytrium* spp. are the source of docosahexaenoic acid (DHA), a dietary supplement used in baby formula (Thirumurugan et al., 2018).

The phylum Actinobacteria is one of the best-known major lineages in the Bacteria domain, constituting one of the biggest taxonomic groups with a variety of recognized species, some of which are well-researched model organisms. Six main classes make up this phylum, which includes a variety of Gram-positive bacteria with various traits and morphologies: *Acidimicrobiia*, *Actinobacteria, Coriobacteria, Nitriliruptoria, Rubrobacteria*, and *Thermoleophilia*. Approximately half of the secondary metabolites found, such as enzymes, antibiotics, immunosuppressive drugs, and anti-tumor drugs, are generated by actinomycetes. Actinobacteria have been recognized as key producers of bioactive natural products since the 1950s. *Streptomyces*, a well-known representative genus of the Actinobacteria class, is the source of more than 70% of economically valuable antibiotics. Additionally, it is astounding that the genus *Streptomyces* is the source of 80% of the actinobacterial natural compounds that have been reported so far. *Streptomycetes* dominate several other microbial groupings in terms of diversity and bioactive potential. For instance, the group of bacteria known as *Streptomycetes* is widely dispersed in both terrestrial and marine settings, and so far, more than 900 species have been found with a validly published name. Additionally, a growing body of research suggests that *Streptomycetes* may live in harsh settings. *Streptomycetes* are believed to have a global distribution because they generate a large number of readily disseminated spores. *Streptomycetes* have a large genome (>7 Mbp), and some of them have been found to have more than 20 gene clusters encoding hypothesized or known biosynthetic pathways. As a result, their potential for biosynthesis is unmatched. Consequently, this enhanced the special potential of *streptomycetes* to produce a variety of new and/or helpful secondary metabolites with antioxidant, anticancer, antibacterial, etc. properties.

Activities that eventually become the main draw for researchers looking into this genus' potential for bioactivity. *Streptomycetes* are confirmed producers of anticancer drugs like bleomycin (glycopeptides group), dactinomycin (non-ribosomal peptides group), mitomycin C (quinones group), and doxorubicin (anthracyclines group), though only a small number of the isolated compounds from microbes can be directly utilized as clinically effective medicines in their own right (naturally occurring form). Natural microbial compounds can also be improved, altered, and developed into significant medicinal leads (Law et al., 2020).

One of the deadliest non-communicable illnesses, cancer is a significant public health problem for people all over the world. By 2040, there will be 29.5 million new cases of cancer and 16.4 million deaths from the disease globally. According to the World Health Organization, cancer is a contributing factor in 1 in 6 fatalities globally, and nearly 70% of cancer-related deaths occur in middle- or low-income nations. Lung, breast, colorectal, prostate, skin, and stomach cancers were the most common types of cancer in 2018, according to the incidence. Cancer incidence rates are rising alarmingly quickly in emerging nations. Additionally, a rising problem in the treatment of cancer is the cancer cells' fast development of drug resistance against currently available therapeutic drugs. Using diverse methods, several research organizations are working to develop or find novel treatments medicines against various malignancies. The search for natural medicines continues to be a primary strategy in the treatment of cancer. It is noteworthy that natural chemicals and their structural analogs/derivatives have made up more than 50%

of authorized medications for the treatment of cancer in the preceding three decades. For the creation of anticancer drugs, natural substances produced from plants, bacteria, fungi, and other marine species are acting as a treasure trove of drug seeds (Mohan et al., 2022). Chemotherapy, radiation therapy, and surgical excision are the usual treatments for tumors. Chemotherapy is primarily useful in the treatment of cancer that has spread to areas of the body other than the original location since surgical procedures and radiation therapy are ineffective in the treatment of metastatic disease. Following Wakesman and Woodruff's and Wakesman's discovery of the first anticancer drug, actinomycin, other microbial metabolites have been shown to have potent anticancer effects in the medical field. About 60% of the substances with anticancer activity come from organic sources. A large number of the chemotherapeutic drugs used to treat cancer are secondary metabolites produced by bacteria, particularly those belonging to the genus *Streptomyces* (Singh et al., 2017). Dr. William Colley was the first to attempt using microbes to cure cancer. For the treatment of sarcoma patients, he combined the culture supernatants of Streptococcus pyogenes and *Serratia marcescens*. The first success in treating inoperable sarcomas came from this approach. Following this, the discovery of therapeutic agents for a variety of human illnesses, including malignancies, has given major attention to bacterium-mediated cancer treatment and chemicals derived from bacteria. Bacterial sources have been used to characterize approximately 13,000 bioactive natural chemicals, demonstrating their unrivaled value as a source of brand-new molecules for drug development. Notably, among the chemicals produced from bacteria, actinomycetes (a category of Gram-positive mycelial bacteria) account for almost 70% of the bioactive compounds. Actinomycetes can therefore be thought of as a factory for secondary metabolites. Furthermore, only 1% of actinomycetes have been grown to date; therefore, it is necessary to bioprospect for physiologically active compounds by collecting actinomycetes and other bacterial species from uncharted areas. Despite the large number of small compounds that have been isolated from these microorganisms, only a limited number of them have undergone rigorous pharmacological investigations (Mohan et al., 2022).

Patients with ulcerative colitis (UC) may have remission after receiving a fecal microbiota transplant (FMT). We sought to uncover bacterial taxonomic and functional characteristics related to response to treatment in a randomized controlled trial of FMT in individuals with active UC. The connection between successful results and the production of alarmone (ppGpp), also known as the stringent response, suggests that FMT may be a stressor on the UC dysbiotic microbiota. Additionally, the nature of the gut's microbial population would probably be significantly impacted by the synthesis of ansamycins, a class of bacteria's secondary metabolites that function as antimicrobial substances against Gram-positive and Gram-negative bacteria, bacteriophages, and certain poxviruses.

Additionally, functional investigations revealed that the species *Eubacterium* and *Roseburia* increased the number of advantageous metabolic pathways. Positive results were specifically connected with metabolic changes to SCFA production (such as pyruvate fermentation to acetate and lactate) and starch breakdown. Since *E. hallii* can generate significant levels of SCFAs, including butyrate and propionate, it has been hypothesized that it is crucial for preserving gut microbial metabolic health and balance. Gut microbial composition would probably be significantly impacted by the synthesis of ansamycins, a class of bacterial secondary metabolites that serve as antimicrobial agents targeting Gram-positive and Gram-negative bacteria, as well as bacteriophages and certain poxviruses (Paramsothy et al., 2019).

3. Cost of Microbial Secendary Metabolites

Any action taken to treat the superbugs imposes significant costs on both individuals and society (Biharee et al., 2020). With the hope of eventually eradicating all infectious illnesses, antibiotics are utilized to treat microbiological infections as well as chemotherapeutic medicines (Jain et al., 2019). These have an antagonistic impact on unrelated bacteria, protozoans,

yeasts, fungi, and viruses and are tiny, cationic, or amphipathic (Richards et al., 2015). Bacteriocins have antibacterial properties in addition to anti-inflammatory, anti-allergic, anti-tumor, and antinociceptive effects (Gomes et al., 2017).

All different kinds of bacteriocins are produced by actinobacteria, but they are highly expensive to make (Hasani et al., 2014). Therefore, recombinant antimicrobial peptide production is taking place in place of chemical synthesis. Since the development of antimicrobial medications, the management of infectious illnesses has been very successful (Hasani et al., 2014).

Additionally, there are a ton of exciting findings in the future of research on fungal endophytes that will help tackle societal and environmental issues in an economical and environmentally acceptable manner (Slama et al., 2021). But certain infections quickly develop resistance to several of the earliest, most powerful medications. These drug-resistant bacteria are becoming more prevalent, which increases morbidity, death, and health care costs. There is a great deal of variation not only between pathogens that cause distinct clinical diseases in various geographic locations but also occasionally in particular areas. Of the five worldwide areas analyzed, the Asia-Pacific region had the greatest rates of antibiotic resistance (Jain et al., 2019).

First-generation antibiotics are no longer effective against bacteria, necessitating the use of second- or third-generation antibiotics, which are sometimes costlier and occasionally hazardous. For instance, the medication required to treat strains of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Mycobacterium* TB that are multi-drug resistant can cost 100 times as much as the first-generation medications used to treat strains that aren't resistant. The fact that resistance to almost all medicines has risen is the most concerning (Procópio et al., 2012). We face an increase in antibiotic choice for infection because of the high expense of clinical studies and the absence of financial incentives for bringing new antibiotics to market (Hegemann et al., 2023). Although scientists have developed technologies that greatly improve the safety of the blood supply, these technologies have drawbacks that prevent their widespread usage, such as higher prices (Domanović et al., 2019).

Additionally, millions of patients who live in underdeveloped countries are unable to pay the increased treatment costs associated with the new antibiotic (Burci & Toebes, 2018). The lack of novel antibiotics encourages the development of complementary therapies, such as herbal therapy, because of its accessibility, cheap cost, and availability (Seukep et al., 2020).

4. Benefit of Microbial Secendary Metabolites

The biological activity of *Aneurinibacillus migulans* isolates was closely connected with the development of a novel gramicidin, according to research by Alenezi et al. The significance of pigments derived from fungus and bacteria and their numerous uses in business and medicine have caught the attention of Narsing Rao et al. A mutation of the deep-sea-derived *Streptomyces* somaliensis was used to produce somalimycin, a novel antimycin-type depsipeptide, in the study by Li et al. Similar to this, Thogersen et al. showed that a maeA mutant of the marine bacterium *Pseudoalteromonas luteoviolacea* produced the possibly antibacterial substances violacein and indolmycin (Singh et al., 2019).

The most prolific makers of antibiotics are *Streptomyces* spp., which have the genetic ability to create 30 secondary metabolites on average. Approximately 80% of the antibiotics in the Actinobacteria phylum come from this genus, and it also generates 2/3 of the antibiotics from natural sources that are now used by the general population. *Streptomycetes* create a lot of secondary metabolites, but when there aren't enough of them, they turn to making aerial hyphae, which are then split into spores that can survive in harsh environments. This is crucial for the effective colonization of *Streptomycetes* in both benign and hostile settings. The vegetative bacterial cell is shielded by streptomycete secondary metabolites, which also play a key function in quorum sensing, heavy metal sequestration, UV protection, and UV resistance.

When the antibiotic actinomycin, which is frequently used as a chemotherapeutic agent for the treatment of a variety of cancers, was discovered

in 1940, it filled the gap left by penicillin, which was ineffective against tuberculosis and some gram-negative pathogens. This led to the discovery of *Streptomycetes* as a source of antibiotics. Two years later, *Streptomyces lavendulae's streptothricin* and *Streptomyces* griseus' streptomycin were identified. Over time, the genus *Streptomyces* produced about 12,400 bioactive substances that were used in medicine and agriculture. Some examples include the immunosuppressant tacrolimus produced by *S. tsukubaensis*, the anti-tumor platenolides obtained from S. platensis, and the insecticide avermectin.

Along with the previously mentioned issues, cancer is a serious health problem and one of the leading causes of mortality, and natural resources have a significant potential to create anti-cancer chemicals. *Streptomyces* species are a good source of anticancer substances. 38 different strains of *Streptomyces* were used in the research of Donald, L., et al., and a total of 82 novel anticancer chemicals were discovered.

It is vitally necessary to develop new antifungal medications to treat infectious disorders brought on by harmful fungi. As drug-resistant fungi continue to evolve, there is an increasing need to discover novel antifungal medications. For instance, it has been demonstrated that the multi-drug-resistant fungus *Candida albicans*, *Aspergillus fumigatus*, and *Candida glabrata* are all resistant to azole medications as a result of changes to their drug binding sites that lower binding affinity. These multi-drug-resistant organisms were similarly unresponsive to additional therapeutic antifungal medications. It's interesting to note that a number of substances derived from *Streptomyces* spp. have antifungal capabilities that might be used to combat drug-resistant and fungal infections (Donald et al., 2022).

Streptomyces are very capable of producing secondary metabolites such as anthelminthic enzymes, herbicides, anti-cancer medications, growth factors including vitamin B12, and immunological modulators (Hasani et al., 2014).

One of the most prevalent pathogens is fungus, and candidiasis accounts for 80% of all fungal infections in hospitals. Additionally, there is a rise in the prevalence of aspergillosis and cryptococcosis, particularly in individuals with immunosuppressed conditions (AIDS, cancer treatment, transplantation). On the other hand, pneumonia, which is primarily what kills AIDS patients, is brought on by *Pneumocystis carinii*. Amphotericin B and nystatin, generated by *Streptomyces* species, are examples of natural polyenes or synthetic azoles that are now used as therapies. Additionally, the echinocandin class's entry into clinics has been a significant development during the past ten years.

More than 30 substances of microbial origin are now being tested in humans at various levels of the clinical development process as anticancer medicines, in addition to recent fungal therapies. Our arsenal of anti-cancer medications includes mitomycins (quinones), bleomycins (glycopeptides), actinomycins (peptides), anthracyclines (aromatic polyketides), pentostatin (nucleosides), and enediynes (polyketides), which are all secondary microbial metabolites produced by actinomycetes, mostly *Streptomyces* strains. As the first antibiotics to be identified from a *Streptomyces* strain in the 1940s, actinomycins are significant historically.

The ester of mycophenolic acid, the first secondary metabolite of microbial origin found, is the most recent immunosuppressant drug to be licensed. From *Penicillium glaucum, Gosio* isolated and crystallized it as a mycotoxin in 1896. Following that, it was used locally as a broad-spectrum topical antibiotic, for instance, to treat psoriasis and associated infections. The first immunosuppressive drug of microbial origin to be introduced was Cyclosporin A, a cyclic undecapeptide produced by the fungus *Tolypocladium niveum*. It has had a significant impact on clinical medicine and is frequently used to prevent and treat graft rejection and graft-versus-host disease after both solid organ and bone marrow transplants. It was fortunate that this team evaluated all of their novel substances for antiviral, cytostatic, and immunosuppressive action because it was initially isolated at Sandoz Laboratories in Basel for its antifungal activity. Although cyclosporin was the sole immunosuppressive drug available for a long time, actinomycetes have

lately made two additional drugs that are 100 times more potent and less harmful. Polyketide macrolactones such as tacrolimus and sirolimus are derived from the bacteria *Streptomyces tsukubaensis* and *Streptomyces hygroscopicus*, respectively. Both of them are antifungal, but by interacting with intracellular proteins and preventing signal transduction, they also prevent T-cell activation and proliferation. Tacrolimus was found in 1984 at Fusjisawa Pharmaceutical Company during a systematic search for drugs with cyclosporin-like action. Its full structural details were discovered in 1987, and it subsequently made its clinical debut in 1991. In 1975, Wyeth-Ayerst Pharmaceuticals discovered sirolimus as a strong anticandida agent. Subsequent research demonstrated sirolimus' excellent anticancer and immunosuppressive effects, and in 1999, the medicine was licensed for use as an immunosuppressive. Additionally, it has anticancer properties, and a rapamycin analog named temsirolimus was recently licensed for the treatment of renal cell carcinoma (Marinelli & Marcone, 2011).

5. Side effects of Microbial Secendary Metabolites

Although secondary metabolites are helpful for medical therapy, including the management of infectious illnesses, their negative consequences must also be taken into consideration. In truth, the world faces the need for the development of innovative, strong small molecules with high anticancer potential and a good safety profile, yet the majority of anticancer medications now used in clinical practice have varying degrees of negative side effects.

Bleomycins, for instance, are a class of antitumor antibiotics with glycopeptide bases that were derived from the bacterium *Streptomyces verticillus* and are used to treat squamous cell carcinomas, melanoma, ovarian cancer, Hodgkin's, and non-Hodgkin's lymphoma. When compared to other medications, bleomycin causes significantly less bone marrow suppression. The clinical uses of bleomycin are restricted despite their therapeutic effectiveness because possible side effects include lung fibrosis and toxicity. Continual attempts have also been conducted to find bleomycins that have unique structural properties, are physiologically active, and have low toxicity (Mohan et al., 2022). Additionally, studies on the short- and long-term side effects of bleomycin sclerotherapy in vascular malformations demonstrate that it can be a successful treatment for VM with repeat exposure and a low risk of short-term side effects, but that the long-term risks are very concerning. Despite the fact that intralesional bleomycin can be a successful treatment for a range of deep VM and is linked with modest and self-limiting short-term adverse effects, long-term side effects are unclear and can be severe, especially when cumulative dosages in certain people are high (Mack et al., 2018).

In addition, doxorubicin, an anthracycline antibiotic that was first identified in *Streptomyces peucetius*, is a secondary metabolite generated by *Streptomyces peucetius* var. caesius. It is a member of the ANT family. Leukemias, lymphomas, multiple myeloma, breast, endometrial, gastric, liver, ovarian, renal, head and neck, and pediatric cancers are among the human malignancies for which it has been authorized (Mobaraki et al., 2017).

Even while it works, it has severe side effects on healthy cells, dose-limiting myelosuppression, and deadly cardiotoxicity. Doxorubicin is a powerful chemotherapy drug that prolongs cancer patients' lives, but its administration is complicated by cardiotoxicity (Mohan et al., 2022). Twenty years after therapy, cardiotoxicity, an apparent adverse effect of doxorubicin, may manifest as an acute or chronic side effect. For kids who have received doxorubicin treatment, this adverse effect is particularly important. Since this adverse impact limits the dose, increases the severity of the disease, or possibly causes death, it's essential to comprehend how things work. It is believed that oxidative stress served as a mediator for doxorubicin-induced cardiotoxicity (Mobaraki et al., 2017). The accepted theory is that both intrinsic and extrinsic apoptotic pathways were triggered by doxorubicin-induced oxidative stress, resulting in cardiomyocyte apoptosis (Aleman et al., 2007). It appeared that doxorubicin could induce apoptosis through a mechanism that would not include ROS formation and oxidative stress di-

rectly, although apoptosis generated free radicals by itself (Mobaraki et al., 2017).

The group of drugs known as actinomycins includes actinomycin D, commonly known as Dactinomycin. *Streptomyces* parvulus and *Streptomyces* antibioticus are the two strains that manufacture it. From diverse microbiological sources, more than 40 actinomycins, including the N-demethylactinomycins and actinomycins C, D, G, F, Y, and Z, have been isolated (Liu et al., 2017). Actinomycin D has been authorized for the treatment of human malignancies such as locally recurrent solid tumors, Wilms tumor, choriocarcinoma, testicular cancer, Ewing sarcoma, and rhabdomyosarcoma as a single agent or in combination with additional medications (Falzone et al., 2018). Actinomycin D has been used as an anticancer treatment for a variety of malignancies, but its use has been restricted because of its hazardous side effects, which include tissue necrosis, myelosuppression, dermatotoxicity, and gastrointestinal enterotoxicity. It revealed considerable tumor regression in pancreatic and stomach cancer xenografts and showed synergetic cytotoxicity with RG7787 (an immunotoxin that is in clinical trials against refractory mesothelioma and pancreatic cancer) in mesothelin-positive cancer cell lines (Mohan et al., 2022).

Antibiotics have played a crucial role in the treatment of infectious illnesses ever since penicillin was discovered. The imminent exhaustion of the medication pipeline and the emergence of antibiotic multi-resistance, however, raise serious questions about how infections will be treated in the future (Singh et al., 2017). Simple-to-fatal responses like strained breathing and asthmatic attacks can range in intensity when it comes to antibiotic side effects. The most frequent adverse effects of antibiotics include feeling ill, diarrhea, and illness. Due to the loss of beneficial bacteria, there may also be oral and digestive system infections. The development of kidney stones caused by sulfonamides, increased light sensitivity caused by tetracyclines, blood coagulation caused by cephalosporins, deafness caused by erythromycin, blood problems caused by trimethoprim, and others are more severe side effects of antibiotics. In addition to causing severe diarrhea in elderly people, penicillin, erythromycin, and cephalosporins can also induce colitis. Penicillin in particular can cause swelling of the tongue and cheeks, rashes, and breathing difficulties as side effects, which are frequently brought on by antibiotic allergies. Superbugs like *Staphylococcus aureus*, known for their deadly resistance, cause over 90,000 deaths annually. The adverse effects of certain antibiotics are shown in the table below (Hassan et al., 2012).

Table 1 .Some Antibiotics and their Potential side effect (Hassan et al., 2012)

Antibiotic name	Potential side effect
Amino glycosides	Hearing loss, Vertigo, Kidney damage
Cephalosporin	Gastrointestinal upset and diarrhea Nausea, Allergic reactions
Penicillin	Gastrointestinal upset and diarrhea Allergy with serious anaphylactic reactions, Brain and kidney injure (rare)
Sulfonamide	Nausea, vomiting, and diarrhea Allergy (including skin rashes) Crystals in urine Kidney failure Decrease in white blood cell count Sensitivity to sunlight
Tetracycline	Gastrointestinal upset, Sensitivity to sunlight, Possible toxicity to the mother and fetus during pregnancy.

6. Conclusion

Secondary bioactive substances from microbial microorganism sources frequently show a wide range of activity against pathogenic species and frequently have immunomodulatory effects on people. The tremendous diversity of naturally occurring chemicals formed from microorganisms offers incredibly different chemical structures that might provide both new antibacterial action mechanisms and new targets inside the bacterial cell. The quick advancement of contemporary biotechnologies also makes it possible to get bioactive chemicals in a way that is low-toxic and beneficial to the environment. We will be able to both detect and identify even extremely low quantities of active substances and elucidate the precise molecular pathways behind their effect(s) on bacterial targets thanks to recent developments in bio screening research, including omics technologies, foremost metabolomics. The chemical modification of potentially beneficial substances to enhance their antibacterial capabilities and lessen their toxicity and side effects is another crucial and promising area.

References

Aleman, B. M., van den Belt-Dusebout, A. W., De Bruin, M. L., van't Veer, M. B., Baaijens, M. H., Boer, J. P. D., ... & van Leeuwen, F. E. (2007). Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood, 109(5), 1878-1886.

Andryukov, B., Mikhailov, V., & Besednova, N. (2019). The biotechnological potential of secondary-metabolites from marine bacteria. Journal of Marine Science and Engineering, 7(6), 176.

Baral, B., Akhgari, A., & Metsä-Ketelä, M. (2018). Activation of microbial secondary metabolic pathways: Avenues and challenges. Synthetic and Systems Biotechnology, 3(3), 163-178.

Biharee, A., Sharma, A., Kumar, A., & Jaitak, V. (2020). Antimicrobial flavonoids as a potential substitute for overcoming antimicrobial resistance. *Fitoterapia*, 146, 104720.

Burci, G. L., & Toebes, B. (Eds.). (2018). Research handbook on global health law. Edward Elgar Publishing.

Demain, A. L. (2014). Importance of microbial natural products and the need to revitalize their discovery. Journal of industrial microbiology and biotechnology, 41(2), 185-201.

Domanović, D., Ushiro-Lumb, I., Compernolle, V., Brusin, S., Funk, M., Gallian, P., ... & Rebulla, P. (2019). Pathogen reduction of blood components during outbreaks of infectious diseases in the European Union: an expert opinion from the European Centre for Disease Prevention and Control consultation meeting. *Blood transfusion*, 17(6), 433.

Donald, L., Pipite, A., Subramani, R., Owen, J., Keyzers, R. A., & Taufa, T. (2022). Streptomyces: Still the biggest producer of new natural secondary metabolites, a current perspective. Microbiology Research, 13(3), 418-465.

Edemekong, P. F., & Huang, B. (2017). *Epidemiology of prevention of communicable diseases*.StatPearls Publishing.

Falzone, L., Salomone, S., & Libra, M. (2018). Evolution of cancer pharmacological treatments at the turn of the third millennium. *Frontiers in pharmacology*, 9, 1300.

Gomes, G. B., Hutson, K. S., Domingos, J. A., Chung, C., Hayward, S., Miller, T. L., & Jerry, D. R.(2017). Use of environmental DNA (eDNA) and water quality data to predict protozoan parasites outbreaks in fish farms. Aquaculture, 479, 467-473.

Gorlenko, C. L., Kiselev, H. Y., Budanova, E. V., Zamyatnin Jr, A. A., & Ikryannikova, L. N. (2020). Plant secondary metabolites in the battle of drugs and drug-resistant bacteria: new heroes or worse clones of antibiotics?. Antibiotics, 9(4), 170.

HabibiSaravi, R., Khankeh, H., Azar, A., & Ghasemihamedani, F. (2019). Communicable diseases surveillance system in Iran: Strengths and weaknesses 30 years following its implementation. Health in Emergencies and Disasters Quarterly, 5(1), 25-36.

Hassan, M. A., Kamal, Y. E. S., Ramlan Aziza, M. R. S., & Hesham, A. (2012). Antibiotics as microbial secondary metabolites: Production and application. J Sci Eng 2012; 59 (1): 101, 111.

Hasani, A., Kariminik, A., & Issazadeh, K. (2014). *Streptomycetes*: characteristics and their antimicrobial activities. Int. J. Adv. Biol. Biomed. Res. 2, 63–75.

Hegemann, J. D., Birkelbach, J., Walesch, S., & Müller, R. (2023). Current developments in antibioticdiscovery: Global microbial diversity as a source for evolutionary optimized anti-bacterials. EMBO reports, 24(1), e56184.

Horak, I., Engelbrecht, G., van Rensburg, P. J., & Claassens, S. (2019). Microbial metabolomics: essential definitions and the importance of cultivation conditions for utilizing *Bacillus* species as bionematicides. Journal of Applied Microbiology, 127(2), 326-343.

Jain, C., Khatana, S., & Vijayvergia, R. (2019). Bioactivity of secondary metabolites of various plants: a review. Int. J. Pharm. Sci. Res, 10(2), 494-504.

Kumar, V., Ahluwalia, V., Saran, S., Kumar, J., Patel, A. K., & Singhania, R. R. (2021). Recent developments on solid-state fermentation for production of microbial secondary metabolites: Challenges and solutions. *Bioresource Technology*, 323, 124566.

Law, J. W. F., Law, L. N. S., Letchumanan, V., Tan, L. T. H., Wong, S. H., Chan, K. G., ... & Lee, L. H. (2020). Anticancer drug discovery from microbial sources: The unique mangrove *streptomycetes*. *Molecules*, 25(22), 5365.

Liu, M., Jia, Y., Xie, Y., Zhang, C., Ma, J., Sun, C., & Ju, J. (2019). Identification of the actinomycin D biosynthetic pathway from marine-derived *Streptomyces costaricanus* SCSIO ZS0073. Marine drugs, 17(4), 240.

Mack, J. M., Richter, G. T., Becton, D., Salem, O., Hill, S. E., & Crary, S. E. (2018). Short-term side effects and patient-reported outcomes of bleomycin sclerotherapy in vascular malformations. Pediatric Blood & Cancer, 65(6), e27008.

Marinelli, F., & Marcone, G. L. (2011). 3.26–Microbial Secondary Metabolites. Comprehensive Biotechnology. Elsevier.

Mobaraki, M., Faraji, A., Zare, M., Dolati, P., Ataei, M., & Manshadi, H. D. (2017). Molecular mechanisms of cardiotoxicity: a review on major side-effect of doxorubicin. Indian J. Pharm. Sci, 79, 335-344.

Mohan, C. D., Rangappa, S., Nayak, S. C., Jadimurthy, R., Wang, L., Sethi, G., ... & Rangappa, K. S.(2022, November). Bacteria as a treasure house of secondary metabolites with anticancer potential. In Seminars in cancer biology (Vol. 86, pp. 998-1013). Academic Press.

Paramsothy, S., Nielsen, S., Kamm, M. A., Deshpande, N. P., Faith, J. J., Clemente, J. C., ... & Kaakoush, N. O. (2019). Specific bacteria and metabolites associated with response to fecal microbiota transplantation in patients with ulcerative colitis. Gastroenterology, 156(5), 1440-1454.

Procópio, R. E. D. L., Silva, I. R. D., Martins, M. K., Azevedo, J. L. D., & Araújo, J. M. D. (2012).Antibiotics produced by Streptomyces. Brazilian Journal of Infectious Diseases, 16, 466-471.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., ... & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in medicine*, 17(5), 405-423.

Ruiz, B., Chávez, A., Forero, A., García-Huante, Y., Romero, A., Sánchez, M., ... & Langley, E. (2010). Production of microbial secondary metabolites: regulation by the carbon source. Critical reviews in microbiology, 36(2), 146-167.

Seukep, A. J., Kuete, V., Nahar, L., Sarker, S. D., & Guo, M. (2020). Plant-derived secondary metabolites as the main source of efflux pump inhibitors and methods for identification. Journal of pharmaceutical analysis, 10(4), 277-290.

Singh, R., Kumar, M., Mittal, A., & Mehta, P. K. (2017). Microbial metabolites in nutrition, healthcare and agriculture. 3 Biotech, 7, 1-14.

Singh, B. P., Rateb, M. E., Rodriguez-Couto, S., Polizeli, M. D. L. T. D. M., & Li, W. J. (2019). Microbial secondary metabolites: recent developments and technological challenges. Frontiers in microbiology, 10, 914.

Singla, R. K. (2020). Secondary metabolites as treatment of choice for metabolic disorders and infectious diseases and their metabolic profiling: part 1. Current Drug Metabolism, 21(7), 480-481.

Shen, B., & Singla, R. K. (2020). Secondary metabolites as treatment of choice for metabolic disorders and infectious diseases & their metabolic profiling-part 2. Current Drug Metabolism, 21(14), 1070-1071.

Slama, H. B., Chenari Bouket, A., Alenezi, F. N., Pourhassan, Z., Golińska, P., Oszako, T., & Belbahri,L. (2021). Potentials of endophytic fungi in the biosynthesis of versatile secondary metabolites and enzymes. Forests, 12(12), 1784.

Thirumurugan, D., Cholarajan, A., Raja, S. S., & Vijayakumar, R. (2018). An introductory chapter: secondary metabolites. Secondary metabolites-sources and applications, 3-21.

Webber, R. (2019). Communicable diseases: a global perspective. Cabi.