Nepal Journal of Biotechnology
Publisher: Biotechnology Society of Nepal
Journal Homepage: https://nepjb.com/index.php/NJB
ISSN (Online): 2467-9313
ISSN (Print): 2091-1130

Harnessing *Bacillus* Species for Antibiotic Discovery: A Review

Daniel Tunde Abbey, Aisha Tajudeen Oganija, Onyibo Leonard Ebube, Dim Emmanuel Ifeanyi
Department of Microbiology and Biotechnology, Federal University Dutse, PMB 7156 Dutse, Nigeria

Received: 08 Aug 2024; Revised: 24 Oct 2024; Accepted: 11 Nov 2024; Published: 31 Dec 2024

Abstract

The genus *Bacillus* is a group of rod-shaped, gram-positive bacteria known for their vast potential of the production of antibiotics. This review examines the potentials of various *Bacillus* species in the production of antibiotics. There is a global threat of antimicrobial resistance and have spurred the need in scientific research for novel antibiotics and *Bacillus* species offers a ray of hope in the discovery of novel antibiotics. Notable among the antibiotics produced by *Bacillus* species include fengycin, gramicidin, iturin, polymyxin, subtilin, difficidin, surfactin, megacin, lichenysin, bacitracin, cerein, pumilicin, circulin, each with greater stability and wide spectrum of activity against gram-positive as well as gram-negative bacteria, fungi. This review highlights the various *Bacillus* species with antibiotics producing abilities such as *B. subtilis, B. polymyxa, B. cereus, B. pumilus, B. megaterium, B. circulans*, the antibiotics produced by these *Bacillus* species, mechanisms of actions of these antibiotics, potential application in medicine, agriculture, biotechnology and industry. *Bacillus* species with antibiotics producing potentials can be applied in combatting the threat posed by antibiotic-resistant pathogens as well as multi-drug-resistant pathogens.

Keywords: Antibiotics, *Bacillus* species, antibiotics discovery, secondary metabolites, antimicrobial resistance.

Corresponding author, email: danielabbey020@gmail.com

Introduction

The growing concern about antimicrobial resistance has led to various research being undertaken to discover novel antimicrobial agents. It is estimated that over 4000 antibiotics have been developed, however, only 50 has been ethically approved for treatments in humans and animals accounting for just 13 percent [1].

Antibiotics are substances produced by a microorganism that has an inhibitory effect or capable of eradicating or eliminating another microorganism. In the 20th century, Sir Alexander Fleming discovered penicillin. Over the years, antibiotic resistant bacteria surfaced posing a significant challenge to infection treatment [2]. As a result, research have been carried to search for novel antibiotics. *Bacillus* species have been identified with their abilities to produce antibiotics thereby making them very instrumental in the fight against infectious diseases and a beacon of hope in the discovery of novel antibiotics in tackling antibiotics resistance [3].

Bacillus species are gram-positive, rod shaped, aerobic or facultatively anaerobic bacteria belonging to class1 of the phylum Firmicutes in other words bacilli (rod shaped) which are ubiquitous in their nature having the ability to survive in varying range of environment including the soil, air and even very extreme environmental condition [2,4].. *Bacillus* species are generally found in soil. *Bacillus* is a spore forming bacteria which makes them resistant to desiccation, which it uses as a means of survival in extreme conditions and as such having the potentials of harboring bioactive compounds. The spores produced by *Bacillus* have been used as probiotics in such a way that it is beneficial to the health and wellbeing of people when administered in the prescribed amount [5,6]. Most Bacillus species are nonpathogenic degrading dead and decaying materials. Members of the Bacillus species include *Bacillus subtilis, Bacillus cereus, Bacillus thuringiensis, Bacillus lichenformis* have been discovered to have antibiotics producing potentials [7].

The review aims to contribute significantly on existing knowledge on the diversity of *Bacillus* species with antibiotics producing potentials and future applications of these antibiotics in medicine in combating antibiotic resistance and improvement of infectious treatment, and addressing global health challenges prevention of agricultural pest and diseases and the industry.

Diversity of Antibiotic Producing *Bacillus* species

Bacillus species can be found to thrive in various environments ranging from air, water, soil and in some cases, extreme conditions such as hot springs, hydrothermal vents, and polar region. A diversity of antibiotics producing *Bacillus* species is found in the soil. Notable among them are *B. subtilis, B. cereus, B. lichenformis, B. thuringiensis, B. polymyxa. B. pumilus, B. megaterium, B. circulans, B. brevis* [4,7].

Bacillus cereus

B. cereus is a gram-positive, rod-shaped bacteria. *B.* cereus is abundant in the soil and water. *B. cereus* plays a very crucial role in decomposing organic matters and also recycling nutrients within the soil [8]. *B. cereus* is a facultative anaerobe and have the capabilities of producing a variety of enzymes such as proteases, lipases, amylases which is paramount for degrading organic matters. *B. cereus* have been known to produce antibiotics and other secondary metabolites that can inhibit the growth of pathogenic and other microorganisms, a mechanism employed by *B. cereus* as a survival mechanism [9]. *B. cereus* form symbiotic relationships with plants improving the fertility of the soil as well as nutrient availability. *B. cereus* contribute vastly to the stability of the soil through the formation of extra cellular polymeric substances.

Bacillus subtilis

B. subtilis is a gram-positive bacterium majorly found in the soil. *B.* subtilis have been identified to produce certain secondary metabolites that are antimicrobial in nature [8,10]. In the soil, *B. subtilis* is essential in biogeochemical cycling and interacts with other soil microorganisms. The secondary metabolites produced by *B. subtilis* makes them out compete other microorganisms in the soil. However, the precise role of *B. subtilis* in the natural environment is still being studied [11,12].

Bacillus lichenformis

B. lichenformis is gram-positive, mesophilic bacilli. *B. lichenformis* have the ability to develop spores which can make them survive harsh environmental conditions. *B. lichenformis* is very important in the industries as they are used to produce enzymes. *B. lichenformis* is also used in biofuel production, bioremediation. *B.* lichenformis have also being studied for the production of antibiotics which have an inhibitory effects against pathogenic microorganisms [2,4,12].

Bacillus polymyxa

B. polymyxa is a gram-positive motile bacterium. *B. polymyxa* produces the antibiotic polymyxin B. *B. polymyxa* promotes the growth of plants. *B. polymyxa* plays a crucial role in the agricultural sector through the process of facilitating nitrogen fixation, phosphate solubility, as well as their antimicrobial properties. *B. polymyxa* degrade major components of lignin, cellulose, hemicellulose [11,13].

Bacillus thuringiensis

B. thuringiensis is a species of the *B.* genus abundant in the soil and have the potentials of producing toxins which are potent to insects. *B. thuringiensis* improves the growth of plants and are used as an effective alternative to fertilizers and pesticides due to the production of antimicrobial agents [14]. They improve plants growth through nitrogen fixation, improving the solubility of phosphate and plant hormone production [15,16].

Bacillus megaterium

B. megaterium is a gram-positive, aerobic and a spore forming bacterium found in various environs including the soil. *B. megaterium* is a mesophilic bacterium [17].*B. megaterium* have been found to produce antibiotics such as penicillin amidase which is a major component for the production of penicillin as well as several enzymes such as amylases used in the baking industry [18]. *B. megaterium* also produces several amino acid dehydrogenases and other molecules with certain antifungal and antiviral potentials. *B. megaterium* is used as biocontrol agents of plant diseases. Some strains of *B.* megaterium have been identified in improving plant growth through the process of nitrogen fixation [19]

Bacillus pumilus

B. pumilus is vastly distributed in the soil, water and on the surfaces of plants and have the ability to thrive in extreme weather conditions making it a spore former. *B. pumilus* is an aerobic bacterium. However, it can grow anaerobically by the process of fermentation [20,21]. Various enzymes have been attributed to *B. pumilus* notable among them are cellulases, proteases, amylases and these enzymes have been applied in industrial settings. *B. pumilus* is a producer of antimicrobial peptides such as pumilicin which exhibits a great spectrum of activity against pathogenic as well as multidrug resistant strains [21,22].

Bacillus circulans

B. circulans is a gram-positive, rod-shaped, spore forming bacteria. The bacterium possess abilities to produce a range of enzymes and antimicrobial compounds. The colonies are usually white or off-white and have a circular appearance, which is reflected in the species name "circulans" [23]. This bacterium is facultatively anaerobic and can metabolize a wide variety of substrates, making it highly versatile in different environments [24]. The bacterium produces antimicrobial substances that can inhibit the growth of other microorganisms, making it a subject of interest for the development of new antibiotics and biocontrol agents [25].

Bacillus brevis

B. brevis cells are rod-shaped and motile due to the presence of flagella. They form endospores, which allow them to survive in harsh conditions making them prolific producers of antibiotics [26]. One of the most notable features of *B. brevis* is its ability to produce peptide antibiotics, such as gramicidin. These antibiotics exhibit great spectrum of activity and stability particularly effective against gram-positive bacteria and are used in topical applications due to their toxic effects when ingested [27]

Antibiotics Produced by *Bacillus* species

Bacillus species have been known to produce various range of antibiotics which is essential for their survival and other interactions with other organisms.

Gramicidin

Gramicidin S is one of the antimicrobial peptides produced by *Bacillus* species. It is very effective against pathogenic bacteria, viruses, and fungi. Squibb and company in the year 1950 discovered Gramicidin. Gramicidin is a class of polypeptide antibiotics. The members of the Gramicidin family include Gramicidin A, B, C, and S. However, these class of gramicidin antibiotics differ in structure as well as their spectrum of activity [26,28]. In the chemical structure of Gramicidin, it comprises two to four amino acids subunit joined by a peptide bond.

Gramicidin is cationic. The hydrophobic nature of the Gramicidin improves the stability and its resistivity to degradation by proteolytic enzymes [26,29]. Gramicidin alters the functions of cellular membranes and as such, Gramicidin S destroys pathogenic bacteria by create pore in the cells and disrupts the normal cell functions. This disruption of the cellular membrane results in the excess leakage of essential ions and molecules thereby leading to the death of the bacteria cells [30]. Gramicidin also inhibits the enzymes essential for the bacteria metabolism. Gramicidin is very effective against gram-positive bacteria such as *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative bacteria such as *Escherichia coli, Pseudomonas aeruginosa* making it a broad-spectrum antibiotic. Gramicidin is very stable in acidic as well as alkaline pH [31]. It is relatively stable in both high a low temperature. Gramicidin is used as a topical antibiotic which has been effective in the treatment of skin infections. Gramicidin is a broad spectrum antimicrobial agent effective against bacteria, viruses and fungi. Gramicidin has a very low toxicity when applied topically. However, Gramicidin exhibit hemolytic activity when used in the system of living organisms [28]

Polymyxin

Polymyxin are a group of antibiotics produced by *Bacillus polymyxa*. Polymyxin was discovered in the year 1940. Polymyxin exists in two classes; Polymyxin B and Polymyxin C. Structurally, Polymyxin compose of a poly cationic peptide ring and a tripeptide side chain with a fatty acid [32]. Polymyxin are very active bactericidal agents and have the mechanism as that of a detergent. Polymyxin acts very effectively against gram-negative bacteria such as *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Salmonella spp, Shigella spp, Citrobacter spp, Enterobacter spp* making it a narrow spectrum antibiotic [33]. gram-negative bacteria are of a lipopolysaccharide layer (LPS). Polymyxin interacts with the lipopolysaccharide layer. The poly cationic peptide ring binds to the outer membrane of the gram-negative bacteria thereby dislodging the calcium and magnesium essential for the stability of the lipopolysaccharide layer [34]. When the calcium and magnesium ions are displaced, the outer membrane is disrupted increasing the permeability of the membrane and the subsequent leakage of the cellular components thereby leading to the occurrence of cell lysis. and the destabilization of the bacteria leading to the cell death [35] Polymyxin just like Gramicidin is also applied topically to treat certain localized skin infections, respiratory infections especially cystic fibrosis patients where is inhaled. Polymyxin has been identified to be very toxic to the human body leading to kidney and brain malfunction and as such, precaution has to be taken during dosing and effective. Polymyxin is only recommended as a last resort when all other antibiotics have failed [35]

Subtilin

Subtilin are groups of antibiotics produced by *Bacillus subtilis*. It is composed of a 32- amino acid pentacyclic lantibiotic [36]. Lantibiotics possess a unique structure comprising of lanthionine as well as methyllanthionine. The formation of lanthionine and methyllanthionine is as a result of the formation of a thioether bonds between cysteine and the dehydrated serine [37]. Several genes are responsible for the formation of the subtilin. These genes include the precursor peptide, modification enzymes, transport proteins, immunity proteins.

Subtilin is very effective against gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pneumoniae, Listeria monocytogenes, Clostridium spp* [38]. Subtilin acts on the bacteria by creating a pore on the cell membrane leading to the leakage of cellular components causing lysis of the cell and the eventual cell death. The bacteria cell uses lipids II which as an important component of the bacteria cell wall synthesis [37,39].

The subtilin binds to the lipid II thereby disrupting the cell wall synthesis leading to the formation of spores. Subtilin is used in topical treatment of skin infections primarily caused by gram-positive bacteria. Since Listeria is a food borne pathogen as very susceptible to subtilin, Subtilin can applied in the food industries as an agent of food preservation. Subtilin is also applied in the agricultural industries as it protects plants from bacterial pathogens thereby improving the growth of plants leading to an increased yield [38,40].

Bacitracin

Various *Bacillus* species have been noted to produce bacitracin most especially *Bacillus lichenformis* and *Bacillus subtilis*. Bacitracin was discovered in the year 1945. Structurally, Bacitracin is composed of a thiazoline ring, peptides and a cyclic peptide backbone [41]. Bacitracin is produced through the non-ribosomal peptide synthetase. Bacitracin is very effective against gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Corynebacterium diphtheriae*. However, bacitracin is impermeable to the outer membrane gram negative bacteria. Its mechanism of actions involves the binding of the carrier lipid molecule which transfers the peptidoglycan precursors through the membrane of the bacteria [41,42].

When such binding has occurred, there is a subsequent dephosphorylation of the bractophenol. This inhibition alters the biosynthesis of the peptidoglycan leading to the lysis of the bacteria cell wall. Bacitracin is used in the treatment of skin infections caused by gram-positive bacteria. It is also applied in the treatment of eyes and ear infections caused by gram-positive bacteria. It is limited to topical usage as a result of the toxicity to the kidney [42,43].

Macrolactin

Bacillus subtilis have been identified to produce macrolactin. Macrolactin is composed of a 24-membered macrolactone ring which is extremely larger than other lactones [44]. Macrolactin is biosynthesized trough the polyketide synthase involving the activity of series of enzymes [45]. Macrolactin is a broad-spectrum antibiotic acting against both gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pneumoniae*, *Bacillus cereus* as well as gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* and viruses such as herpes simplex virus (HSV), and human immunodeficiency virus (HIV) [46]. Macrolactin acts by inhibiting the cell wall synthesis of the bacteria thereby altering the stability of the cell membrane. Macrolactin inhibits the replication in viruses specifically targeting the viral proteins necessary for viral replication.

Macrolactin have been discovered to possess anti-cancer potentials by eliminating cell through cytotoxic effect thereby killing the cancer cells. Macrolactic offers promising solutions against cancer, viral infections as well as resistant bacteria [44,46,47].

Fengycin

Bacillus subtilis particularly produces a lipopeptide antibiotic known as fengycin. Structurally, Fengycin has a lipopeptide ring with about 10 to 17 amino acid peptide chain closely linked to β -hydroxy fatty acid [46]. The biosynthesis of Fengycin is similar to that of Bacitracin which involves the non – ribosomal pathway. Fengycin is highly effective against a variety of fungal species such as *Fusarium spp, Rhizoctonia spp, Alternaria spp, Phytophthora spp* [47]. Its mechanism of activity involves the disruption of the cell membrane leading to the loss of essential cellular components and also interferes with the cell wall synthesis of the fungi. Fengycin is applied in the agricultural industries as a biocontrol agent against fungal diseases and also in the process of seed coating to protect the seeds from fungal pathogens during germination [47,48].

Surfactin

Surfactin is a lipopeptide antibiotics isolated from diverse *Bacillus* species notable among them are *Bacillus subtilis*. Surfactin as the name implies, acts as a biosurfactant. In its structure, Surfactin is made up of 7 amino acids in addition to an L-glutamic acid, L-valine as well as an L-leucine forming a ring shape across a lactone bond [49,50]. Surfactin is synthesized through the non-ribosomal peptide synthetase pathway. Surfactin is a broad-spectrum antimicrobial agent acting against a variety of microorganism including bacteria including gram-positive and gram-negative bacteria, fungi a virus. Surfactin also possess certain anti-inflammatory potentials. Due to the amphiphilic nature of Surfactin, when inserted into the cell membrane, it alters the stability of the membrane leading to the lysis of the cells [51,52]. As a biosurfactant, it lowers the surface tension increasing the solubility and bioavailabity of hydrophobic compounds. Surfactin modulates the immune response preventing the production of cytokines an inflammatory agent. Surfactin can effective in bioremediation to improve the degradation of crude oil spills by increasing their solubility and bioavailabity. Surfactin can be used in detergent making due to its environmentally friendly nature. Surfactin producing

Bacillus strains can be applied as biocontrol agents in preventing plant pathogens and enhancing the growth of plants through nutrients uptake [51,53].

Iturin

Bacillus subtilis and *Bacillus pumulus* have been identified to produce iturin, a lipopeptide antibiotics. Iturin is composed of lipopeptide ring of 7 amino acids closely joined to a fatty acid. Iturin carries out its biosynthesis through the non-ribosomal peptide synthetase which produces various variants of the antibiotics such as mycosubtilin, iturin A, iturin C, and bacillomyxin [44,54]. Iturin are very effective against fungal pathogens such as *Fusarium spp, Aspergillus spp, Candida spp, Rhizoctonia spp*. Iturin exerts its effective by creating pores in the membrane leading to a loss of essential ions thereby causing cell death. Iturin also increases the permeability of the membrane cause an overflow of the cellular contents leading to cell death.[44]. Iturin also inhibits the growth of the fungal pathogen. Iturin is applied in the agricultural sector as a biocontrol agent against fungal pathogens. It can be applied in seed coating to protect germinating seeds from infection from fungal pathogens [54].

Difficidin

Difficidin is a polyketide antibiotic produced from *Bacillus subtilis.* Structurally, difficidin, is composed of a macrocyclic polyene lactone consisting of a hydroxyl or carboxyl group, fused double bond, lactone ring and a polyketide ring structure [53]. Difficidin is biosynthesized through the polyketide synthase pathway. Difficidin is a broad spectrum antibiotic effective against gram-positive bacteria such as *Staphylococcus aureus, Bacillus cereus, Enterococcus faecalis* and gram-negative bacteria such as *Salmonella spp, Escherichia coli, Pseudomonas aeruginosa* and antibiotic resistant strains of bacteria including multi drug resistant bacteria [54].

Difficidin interferes with the protein synthesis of the bacteria. Difficidin fuses with the ribosome of the bacteria thereby altering the translational process necessary for the protein synthesis [13]. When the bacteria protein synthesis has been inhibited, the essential functions of the bacteria cell are disrupted leading to the eventual death of the bacteria. As a result of the broad-spectrum nature of the antibiotics, it offers a ray of hope in tackling antibiotics resistant strains [55].

Thuringiensin

B. thuringiensis is a primary producer of thuringiensin, a secondary metabolite. Thuringiensin is also referred to as β-exotoxin as it is has a very stable nucleotide analogue which is very effective against a wide range of microorganisms such as bacteria, fungi, viruses and also some insecticidal effects. Structurally, thuringiensin is composed of adenine and an arabinose which is closely similar to other nucleotides. Thuringiensin blocks nucleic acid synthesis which is a process essential to all microorganisms [56]. By interfering and subsequent inhibition of RNA polymerase leading to the blockage of the transcription process essential to bacteria, fungi, protozoa, and even insects. Thuringiensin is nonspecific in its mode of action posing a significant threat to non-target organisms. Thuringiensin continues to be a subject of research, particularly in understanding its mechanism of action and exploring its potential uses in biotechnology. Studies have also focused on mitigating its environmental impact and developing more targeted applications [56,57].

Circulin

Circulin a group of cyclic peptides formed as a result of the bonding of peptide to amino acids. *B. circulans* have been identified to produce circulin. The structure is a major contributor to its stability and a greater spectrum of activity against gram-positive bacteria [58]. Circulin acts by disrupting the cellular integrity of the bacteria membrane. When this occurs, there is a leakage of essential cellular constituents which results in cellular death. Due to the cyclic nature of the peptide, it enters into the lipid bilayer of the bacterial membrane creating pores which affects the permeability of the bacterial membrane [59]. Circulin's unique structure and mechanism of action have sparked interest in the development of novel antimicrobial agents. Research continues to explore its potential in various fields, including medicine and agriculture [59].

Pumilicin

Pumilicin is produced by *B. pumilus*. Structurally, pumilicin is a cyclic peptide which contributes significantly to its stability and resistance to degradation by proteolytic enzymes. Pumilicin acts by binding to the lipid layers of the membrane, creating pores that increases the selective permeability of the membrane leading to lysis of cell and subsequent death due to leakage of essential cellular components [22]. Pumilicin is a narrow spectrum antibiotic as it is very effective against gram-positive bacteria such as *Staphylococcus aureus, Bacillus cereus.* Studies suggests its activity against antibiotic resistant strains. Due to its broad-spectrum activity, pumilicin has potential applications in medicine and agriculture. It can be used as a natural preservative

Table 1. Comparison of the Antibiotics Produced from *Bacillus* species showing spectrum of activity and mechanism of action

Antibiotic	Producing *Bacillus* Strain	class of antibiotic	spectrum of activity	mechanism of action.	Reference
Gramicidin	*Bacillus brevis*	Polypeptide	gram-positive and gram-negative bacteria	Inhibition of cell wall synthesis Formation of pores.	[26,28]
Polymyxin	*B. polymyxa*	Polypeptide	gram-negative bacteria	Increased membrane permeability	[32,34]
Subtilin	*B. subtilis*	Lantibiotic	gram-positive bacteria	Formation of pores, Inhibition of cell wall synthesis.	[37,38]
Bacitracin	*B. lichenformis*, *B. subtilis*	Polypeptide	gram-positive bacteria.	Inhibition of peptidoglycan synthesis.	[41,43]
Macrolactin	*B. subtilis*	Lantibiotic	gram-positive bacteria gram-negative bacteria virus	Inhibition of cell wall synthesis., Inhibition of viral replication.	[45,46]
Surfactin	*B. subtilis*	Lipopeptide	gram-positive bacteria gram-negative bacteria	Increased membrane permeability.	[51,52]
Iturin	*B. subtilis* *B. pumulus*	Lipopeptide	fungi pathogens	Inhibition of growth, Inhibition of cell wall synthesis Increased cell permeability.	[44.54]
Difficidin	*B. subtilis*	Polyketide	gram-positive bacteria, gram-negative bacteria multi drug resistant strains.	Inhibition of protein synthesis	[13,53]
Fengycin	*B. subtilis*	Lipopeptide	fungal pathogens	Inhibition of cell wall synthesis Disruption of cell membrane.	[46,48]
Thuringiensin	*B. thuringiensis*	Polyketide	gram-positive bacteria, gram-negative bacteria,multi drug resistant strain.	Inhibition of nucleic acid synthesis	[56,57]
Circulin	*B. circulans*	Polypeptide	gram-positive bacteria	Increased membrane permeability, Formation of pores	[59]
Pumilicin	*B. pumilus*	Polypeptide	gram-positive bacteria	Increased membrane permeability, Formation of pores	[22,60]
Cerein	*B. cereus*	Polypeptide	gram-positive bacteria	Formation of pores	[60]
Zwittericin A	*B. cereus*	Aminopolyol	gram-positive bacteria. gram-negative bacteria	Inhibition of protein synthesis.	[62,64]
Lichenysin	*B. lichenformis*	Lipopeptide	gram-positive bacteria	Increased membrane permeability.	[65,66]

in food and as a therapeutic agent in treating bacterial infections [22,60].

Cerein

Cerein is a small peptide antibiotic produced by *B. cereus*. It is characterized by its heat-stable nature and broad-spectrum antibacterial activity. The peptide typically consists of 28-34 amino acids and possesses a cationic character, which facilitates its interaction with the negatively charged bacterial cell membranes [22]. The primary mode of action of cerein involves disrupting the bacterial cell membrane. This disruption is achieved through the insertion of the peptide into the lipid bilayer, leading to pore formation and leakage of intracellular components, ultimately resulting in cell death. This mechanism is similar to that observed in other bacteriocins and is effective against a range of gram-positive bacteria, including *Listeria monocytogenes* and *Staphylococcus aureus* [22,61]. Its ability to inhibit the growth of foodborne pathogens like *Listeria monocytogenes* makes it a promising candidate for food preservation and safety. Additionally, cerein has shown potential in clinical applications for treating infections caused by antibiotic-resistant bacteria. Its stability and efficacy make it an attractive option for developing new antimicrobial agents and bio preservatives [61].

Zwittermicin A

Zwittermicin A is an antibiotic produced by *Bacillus cereus*. Zwittermicin A is a novel aminopolyol antibiotic characterized by its zwitterionic nature, which means it contains both positive and negative charges at physiological pH. This compound consists of a long linear chain with amino and hydroxyl groups, making it water-soluble and distinct from other antibiotics. Zwittericin A acts by inhibiting the initiation and elongation steps of translation, thereby preventing the production of essential proteins [62]. Additionally, zwittermicin A has been observed to interfere with cell wall synthesis, further contributing to its antibacterial activity. This dual mechanism makes it effective against a wide range of gram-positive and gram-negative bacteria such as *Escherichia coli* and *Pseudomonas syringae* including certain antibiotic-resistant strains [63]. Its ability to target multiple bacterial processes makes it a valuable agent in the development of new antibiotics, especially in the era of rising antibiotic resistance [64].

Lichenysin

Lichenysin is a biosurfactant produced by *B. licheniformis* due to its potentials to produce stable emulsions which have a very potent surface-active capability. Lichenysin is a cyclic lipopeptide consisting of a peptide ring of seven amino acids linked to a hydrophobic fatty acid chain. The fatty acid chain contributes to its amphipathic nature, enabling it to reduce surface and interfacial tensions effectively. This structure is crucial for its biosurfactant properties, allowing it to aggregate at interfaces, thereby reducing surface tension and stabilizing emulsions [65]. The amphipathic nature of lichenysin allows it to insert into lipid bilayers, disrupting the integrity of cell membranes. This action can lead to cell lysis, particularly in gram-positive bacteria. Its surface-active properties also facilitate the emulsification of hydrophobic substances, making it useful in applications such as bioremediation, where it can enhance the breakdown of hydrophobic pollutants [65,66]. lichenysin can be used in bioremediation to treat oil spills and other environmental contaminants. Its thermal stability and effectiveness at extreme pH levels make it suitable for various environmental conditions [66].

Regulation of Antibiotic Production by *Bacillus* species

The antibiotics producing potential of *Bacillus* species is strictly by various factors notable among them are the genetic regulation and the environmental regulation [67]

Genetic Regulation

The genetic regulation of the antibiotics production in *Bacillus* species involves a series of steps which involves the transcriptional mechanism, post transcriptional mechanism and the epigenetic mechanism [1]. In the transcriptional mechanism, regulatory genes are formed. A cluster of genes which are packed called operons. The operons are responsible for the production of antibiotics as seen in the production of a lipopeptide called surfactin [68].

In other cases, certain *Bacillus* strains use a two-component regulatory system to biosynthesize their antibiotics. The two-component system called the kinase sensor and the regulator response. *Bacillus subtilis* produces the surfactin through the two-component system ComP-ComA which is used to biosynthesize the sarcastic a very potent antibiotic [12,37].

In the post transcriptional phase, tiny ribonucleic acid RNA is applied to regulate the integrity and the translation of mRNA encoding enzymes. The tiny RNA targets the mRNA and degrade it making the translation process very seamless. Certain binding proteins are very essential in the post transcriptional phase as the binding proteins binds to the mRNA severely affecting its translation as a result, more antibiotics are produced [68]

In the epigenetic regulation, DNA is methylated. As a result of the methylation, RNA polymerase is inhibited and as such, antibiotics producing genes are the synthesized. In some rare cases *Bacillus* species produce histone like proteins. These proteins affect the chromosomal structure of the bacterial cell thereby leading to the synthesis of antibiotics producing genes [69]

Environmental Regulation

Nutrient availability plays a crucial role in the production of antibiotics by *Bacillus* species. When nutrients are readily available, the genes responsible for the production of antibiotics are synthesized. *Bacillus* species have the ability to sense environments rich in abundant nutrients and as such, antibiotics are produced to outcompete other microorganisms as a means of survival [34]

The production of antibiotics is highly affected by the presence of certain environmental stress factors such as stress due to excess oxidation, shock as a result of heat and stress due to osmotic pressure has a significant impact on the antibiotics producing potentials of *Bacillus* species [70]. When environmental stress is sensed, a response from stress regulators is induced, when such response is induced, the genes responsible for the production of antibiotics are controlled so as not to cause harm to the *Bacillus* species [68,70]

Application of Antibiotics Producing *Bacillus*

Critically understanding the potentials of *Bacillus* species in the production of antibiotics is crucial as its application can be very beneficial to various sector of our endeavor. Antibiotics producing *Bacillus* species can be applied in various setting including in agriculture, biotechnology, industries and in medicine.

In Medicine

Antibiotics produced from *Bacillus* species can be applied in the treatment of infections caused by bacteria and even bacteria known to be resistant against other antibiotics [44]. It can also be applied as a preservative of some pharmaceutical products to prevent it from microbial contamination [28]. Antibiotic such as polymyxin can be applied as inhalation therapy to treat respiratory infections especially in patients with cystic fibrosis and offers a ray of hope in the treatment of multidrug resistant bacteria [32]. Bacitracin can be applied in the treatment of bacterial infections of the eyes such as conjunctivitis. It can also be applied in preventing infections that may results due to cuts and scraps [13] Macrolactin can be applied in the treatment of viral diseases as a result of its ability to inhibits the viral replication of proteins [42].

In Industries

Subtilin an antibiotic produced by *Bacillus subtilis* can be applied as a food preservative in food industries as it is very effective against *Listeria monocytogenes* a food borne pathogen [10]. Macrolactin can be applied in the food industries as natural preservatives thereby increasing the shelf life of food and improving the quality and safety of food [49]. Surfactin can be applied in the production of detergents and other cleaning agents due to its environmentally friendly nature [46].

In Biotechnology

Surfactin due to its properties as a biosurfactant can be applied as a biotechnological tool in bbioremediation of oil spills as it increases the solubility and bioavailability of hydrophobic compounds [31]. As a result of the interaction of Subtilin with the lipid II, such mechanism can be studied and can be applied in making biosensors which can be utilized in the visualization of contamination due to bacteria pathogens [36] In the fermentation process, Subtilin can be applied in bioreactors to prevent bacterial contamination during the process of fermentation [35]. Difficidin a broad-spectrum antibiotic can be effectively applied a research tool to study the function of the bacterial ribosome thereby understanding the process of resistance development [43].

In Agriculture

Certain *Bacillus* species produce antifungal agents such as Fengycin and iturin which can be used to protect crops from fungal pathogen and diseases induced by such pathogens [44]. Antibiotics such as Fengycin can be applied to coat seeds of plants prior to planting to provide protection to the seeds from fungal pathogens and improving their germination [33].

Challenges and Limitation of Antibiotics Producing *Bacillus* species

Microorganisms are constantly evolving and with time may develop resistance to the antibiotics produced by *Bacillus* leading to research for a novel compound for combating resistant microorganisms.[71] emphasized on the need for ensuring safety and ethical consideration and all regulatory approval before use in particular in agriculture and food producing industries. Certain antibiotics produced by *Bacillus* species (gramicidin S and Polymyxin are in limited use and only applied as the last resort due to their nephrotoxicity and neurotoxicity [31,72].

Fermentation process are not fully optimized and as such, it remains a challenge in industries to ensure full production an equitable distribution [43]. Poor storage facilities in ensuring the stability and standard of purification of the antibiotics poses a serious challenge [73,74].

Conclusions.

Diverse strain of *Bacillus* species has been identified to produce certain antibiotics such *B. polymyxa, B. subtilis, B. lichenformis, B. pumulus, B. brevis*. The antibiotics produced include gramicidin, polymyxin, fengycin, iturin, subtilin, surfactin, macrolactin, difficidin. These antibiotics are biosynthesized through various pathways which is regulated by a combination of both genetic and environmental factors such as nutrient availability, temperature. These *Bacillus* have devised means to resist harsh environmental conditions. By carefully understanding the mechanisms involved in the antibiotics producing process, it can be applied in various sectors of our daily endeavors including in medicine, in biotechnology, in agriculture and in industries. It is of paramount importance that continued research be carried out on antibiotics producing *Bacillus* so effective and long-lasting solutions can be applied in improving the health of the people as well as environmental sustainability, food security.

Future Prospects.

Production process of the antibiotics should be fully optimized to increase the yield and efficient distribution. Regulatory approval should be issued to antibiotics derived from *Bacillus* species essentially in agriculture and food industries. New derivatives of toxic *Bacillus* antibiotics such as gramicidin and polymyxin should be produced with effective antimicrobial potentials but with a reduced level of toxicity. Effective storage facilities should be developed in improving the stability of the antibiotics. Further research should be carried out into the mechanisms of these antibiotics in order to understand how these antibiotics can be optimized for effectiveness. Some *Bacillus* species have not been effectively studied and as such, these antibiotics can have unique characteristics and the potentials of certain antibiotics.

Author's contribution

DA, conceptualized and wrote this manuscript, AO, edited this manuscript, LO and DE, assisted in literature search and proofreading.

Competing interest

The authors declare no competing interest

Acknowledgement

Our sincere gratitude to the Microbiology and Biotechnology Department, Federal University Dutse.

References

1. Baek, K.H., Lee, S., Kim, H.S. *Biosynthesis, molecular regulation, and application of bacilysin produced by Bacillus species*.2022;2(5), 397. Retrieved from [MDPI](https://www.mdpi.com/2218-1989/12/5/397)
2. Sitotaw, B., Ayalew, F., Girma, A., Mekonnen, A. B., Bin Jardan, Y. A., Nafidi, H. A., & Bourhia, M. Isolation and identification of promising antibiotic-producing bacteria. *Open Chemistry*, 2022;*20*(1), 1283–1291. https://doi.org/10.1515/chem-2022-0233
3. Tom, K. T., Lexa, G. M., George, O., & Francis, G. Isolation and characterization of antibiotic producing *Bacillus* species in Lake Bogoria, Kenya. *African Journal of Microbiology Research*, 2015;*9*(14), 1037–1043. https://doi.org/10.5897/ajmr2015.7441
4. Thapa, A., Budhathoki, A., Sapkota, A., Sainju, M., & Shrestha, P. Isolation, Identification and Screening of *Bacillus* species with Antimicrobial Activity from Different Soil Samples of Kathmandu Valley. *Nepal Journal of Biotechnology*, 2021;*9*(2), 1–6. https://doi.org/10.54796/njb.v9i2.41892
5. Al-Turk, A., Odat, N., & Massadeh, M. I. Isolation and molecular characterization of antibiotic producing *Bacillus licheniformis* strains isolated from soil. *Journal of Pure and Applied Microbiology*, 2020;*14*(4), 2363–2370. https://doi.org/10.22207/JPAM.14.4.14
6. Abdul, A., & Al-Janabi, H. S. Identification of Bacitracin Produced by Local Isolate of *Bacillus licheniformis*. *African Journal of Biotechnology*, 2006;*5*(18), 1600–1601. http://www.academicjournals.org/AJB
7. Kuta, F. A., Nimzing, L., & Orka'a, P. Screening of *Bacillus* Species with Potentials of Antibiotics Production. In *Applied Medical Informatics Original Research* 2009;(Vol. 24, Issue 2).
8. Sumi, C. D. Antimicrobial peptides of the genus *Bacillus*: a new era for antibiotics. Canadian Journal of Microbiology, 2015;61(2), 93-1
9. Patel, P. Isolation and characterization of antibiotic-producing *Bacillus* strains from soil. International Journal of Current Microbiology and Applied Sciences. 2015; 4(6), 781-788.
10. Stein, T. *Bacillus subtilis* antibiotics: structures, syntheses and specific functions. *Molecular Microbiology*, 2005;*56*(4), 845–857. https://doi.org/10.1111/J.1365-2958.2005.04587.X
11. Singh, A. P., Singh, R. B., & Mishra, S. Studies on Isolation and Characterization of Antibiotic Producing Microorganisms from Industrial Waste Soil Sample. In *The Open Nutraceuticals Journal* 2025;(Vol. 5).
12. Zhang, S., Xu, X., & Zhang, L. Characterization of difficidin biosynthetic gene cluster from *Bacillus subtilis* and heterologous production in *Escherichia coli*. Applied Microbiology and Biotechnology. 2019;103(7), 2911-2921.
13. Gao, P. *Bacillus licheniformis* BL010: a novel plant growth-promoting rhizobacterium that defends its host against Fusarium wilt of banana. Plant Soil. 2017; 421(1-2), 275-287.
14. Branda, S. S., González-Pastor, J. E., Ben-Yehuda, S., Losick, R., & Kolter, R. Fruiting body formation by *Bacillus subtilis*. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;*98*(20), 11621–11626. https://doi.org/10.1073/PNAS.191384198
15. Slepecky, R. A., & Hemphill, H. E. The genus *Bacillus*—nonmedical. In Prokaryotes Springer, New York, NY. 2006;530-562).
16. Raaijmakers, J. M. Antimicrobial compounds produced by *Bacillus* species: applications in plant disease control. 2010;78(4), 337-347.
17. Mondol, M. A. M., Shin, H. J., & Islam, M. T. Diversity of secondary metabolites from marine *Bacillus* species: Chemistry and biological activity. *Marine Drugs*. 2013;*11*(8), 2846–2872. https://doi.org/10.3390/MD11082846
18. Das, S. Characterization of a new bacillomyxin produced by a *Bacillus subtilis* isolate from soil samples. Indian Journal of Microbiology. 2006;48(3), 379-386.
19. Chen, X. H. Comparative analysis of the complete genome sequence of the plant growth-promoting bacterium *Bacillus amyloliquefaciens* FZB42. *Nature Biotechnology*. 2009;25(9), 1007-1014
20. Xue, Y., Jin, L., Gao, Y., & Zhang, J. *Bacillus pumilus* XJ18 produces lipopeptides that are antagonistic against several phytopathogens and shows potential for biocontrol. Microbiological Research. 2020;234, 126422.
21. Schallmey, M., Singh, A., & Ward, O. P. Developments in the use of *Bacillus* species for industrial production. Canadian Journal of Microbiology. 2020; 50(1), 1-17.
22. Bizani, D., & Brandelli, A. Characterization of a bacteriocin produced by a newly isolated *Bacillus sp.* strain 8A. Journal of Applied Microbiology. 2002;93(3), 512-519.
23. Gordon, R. E., Haynes, W. C., & Pang, C. H. The genus *Bacillus*. Agricultural Handbook, 1973;427, 1-283.
24. Priest, F. G. Systematics and ecology of *Bacillus*. In A. L. Sonenshein, J. A. Hoch, & R. Losick (Eds.), *Bacillus subtilis* and Other gram-positive Bacteria: Biochemistry, Physiology, and Molecular Genetics American Society for Microbiology.1993;3-17
25. Ahmed, I., Yokota, A., Yamazoe, A., & Fujiwara, T. Proposal of *Lysinibacillus boronitolerans gen. nov., sp. nov.*, and transfer of *Bacillus fusiformis* to *Lysinibacillus fusiformis comb. nov.* and *Bacillus sphaericus* to *Lysinibacillus sphaericus comb. nov.* International Journal of Systematic and Evolutionary Microbiology. 2013;57(5), 1117-1125.
26. Logan, N. A., & De Vos, P. Genus I. *Bacillus*. In Bergey's Manual of Systematic Bacteriology, Springer, New York, NY. 2009;21-128
27. Shaheen, M., Li, J., Ross, A. C., Vederas, J. C., & Jensen, S. E. *Paenibacillus polymyxa* PKB1 produces variants of polymyxin B-type antibiotics. *Chemistry and Biology*. 2011;*18*(12), 1640–1648. https://doi.org/10.1016/J.CHEMBIOL.2011.09.017
28. Kawulka, K. E., Sprules, T., Diaper, C. M., Whittal, R. M., McKay, R. T., Mercier, P., Zuber, P., & Vederas, J. C. Structure of Subtilisin A, A Cyclic Antimicrobial Peptide from *Bacillus subtilis* with Unusual Sulfur to α-Carbon Cross-Links: Formation and Reduction of α-Thio-α-Amino Acid Derivatives. *Biochemistry*. 2004; *43*(12), 3385–3395. https://doi.org/10.1021/BI0359527
29. Orlowski, M., & Baldwin, T. O. Mechanism of action of gramicidin S synthetase. Journal of Biological Chemistry 1972;247(4), 1422-1431.
30. Sato, H., Takikawa, M., Hoshino, K., & Suzuki, I. Characterization of *Bacillus* strains producing thermo-stable and broad-spectrum bacteriocins. Journal of Microbiology, Biotechnology and Food Sciences. 2020;9(6), 931-936. https://doi.org/10.15414/jmbfs.2020.9.6.931-936
31. Hamamoto, T. The biosynthesis of the cyclic peptide antibiotic gramicidin S in *Bacillus brevis*: natural variation and engineering. Journal of Molecular Microbiology and Biotechnology, 2002;4(3), 193-202
32. Lee, H. J., Kim, J. A., Lee, J. S., & Park, H. G. Characterization of *Bacillus* strains isolated from soil with various thermal

conditions. Journal of Environmental Biology. 2020;41(5), 1261-1269. https://doi.org/10.22438/jeb/41/5/MRN-1
33. Pujato, S. A., Aredes, M. E., Frola, I. D., Giubergia, S. I., & Simonetta, A. C. Subtilin production by *Bacillus subtilis* 6633 isolated from a soybean rhizosphere and its effect on the growth of *Pseudomonas aeruginosa* and *Rhizobium sp*. Research in Microbiology. 2018;169(5-6), 272-281. doi:10.1016/j.resmic.2018.06.001
34. Li, Q., Liao, S., Zhi, H., Xing, D., Xiao, Y., & Yang, Q. Characterization and sequence analysis of potential biofertilizer and biocontrol agent *Bacillus subtilis* strain sem-9 from silkworm excrement. *Canadian Journal of Microbiology*. 2019;*65*(1), 45–58. https://doi.org/10.1139/CJM-2018-0350
35. Velkov, T. Structure, function, and biosynthetic origin of polymyxins: novel insights into the mechanism of action. Antimicrobial Agents and Chemotherapy. 2013;57(10), 4721-4731. doi:10.1128/AAC.00649-13
36. Guder, A., Wiedemann, I., & Sahl, H. G. Post translationally modified bacteriocins - the lantibiotics. Biopolymers. 2000;55(1), 62-73. doi:10.1002/1097-0282(2000)55:1<62: AID-BIP70>3.0.CO;2-8
37. Samrot, A. V., Prasad, R. J. J., Rio, A. J., & Sneha, S. J. Bioprospecting of *Bacillus brevis* isolated from soil. *Recent Patents on Biotechnology* 2015;*9*(1), 42–49. https://doi.org/10.2174/1872208309011511111124333
38. Hammami, R., Fernandez, B., Lacroix, C., & Fliss, I. Anti-infective properties of bacteriocins: an update. Cellular and Molecular Life Sciences. 2007;64, 1138-1156. doi:10.1007/s00018-007-6503-3
39. Cawoy, H., & Debois, D. *Lipopeptides as main ingredients for inhibition of fungal phytopathogens by Bacillus subtilis/ amyloliquefaciens. Microbial Biotechnology* 2015;8(2), 281-295. doi:10.1111/1751-7915.12247
40. Dischinger, J., Basi Chipalu, S., & Bierbaum, G. Lantibiotics: promising candidates for future applications in health care. International Journal of Medical Microbiology. 2014;304(1), 51-62. doi:10.1016/j.ijmm.2013.09.002
41. Kearns, D. B., & Losick, R. Swarming motility in undomesticated *Bacillus subtilis*. *Molecular Microbiology*. 2003;*49*(3), 581–590. https://doi.org/10.1046/J.1365-2958.2003.03584.X
42. Li, M., Li, Y., Li, H., Wen, L., Li, Y., & Zhu, S. Genome sequencing reveals different populations of *Bacillus subtilis* and *Bacillus licheniformis* in poultry-related environments. Animal Nutrition. 2019;5(2), 178-185. https://doi.org/10.1016/j.aninu.2019.01.005
43. Kearns, D. B., Chu, F., Branda, S. S., Kolter, R., & Losick, R. A master regulator for biofilm formation by *Bacillus subtilis*. *Molecular Microbiology*. 2005;*55*(3), 739–749. https://doi.org/10.1111/J.1365-2958.2004.04440.X
44. Ongena, M., & Jacques, P. *Bacillus* lipopeptides: versatile weapons for plant disease biocontrol. Trends in Microbiology. 2008;16(3), 115-125.
45. Gomaa, E. Z. Optimization and characterization of alkaline protease and carboxymethyl-cellulase produced by *Bacillus pumilus* grown on Ficus nitida wastes. *Brazilian Journal of Microbiology*. 2013;*44*(2), 529–537. https://doi.org/10.1590/S1517-83822013005000048
46. Liu, J., Cui, X., Liu, Z., Guo, Z., Yu, Z., Yao, Q., Sui, Y., Jin, J., Liu, X., & Wang, G. The diversity and geographic distribution of cultivable *Bacillus*-like bacteria across black soils of northeast China. *Frontiers in Microbiology*, 2019;*10*(JUN). https://doi.org/10.3389/FMICB.2019.01424/FULL
47. Van Dijl, J. M., & Hecker, M. *Bacillus subtilis*: From soil bacterium to super-secreting cell factory. *Microbial Cell Factories*, 2013;*12*(1). https://doi.org/10.1186/1475-2859-12-3
48. Cao, L., Li, D., Huang, Q., Wei, L., Li, G., & Zhang, S. *Characterization of antibiotic-producing Bacillus species from cow dung. BMC Microbiology.* 2020;20(1), 1-9. https://doi.org/10.1186/s12866-020-01947-5.
49. Heng, G. H., Ibrahim, S., Abu, B., & Tan, W. S. The Role of Surfactin in Biological Control: An Overview. Biotechnology Advances. 2020;39, 107-114.
50. Nicholson, W. L. Roles of *Bacillus* endospores in the environment. *Cellular and Molecular Life Sciences*. 2002;*59*(3), 410–416. https://doi.org/10.1007/S00018-002-8433-7
51. Dang, Q., Zhao, W., Yang, B. Regulation, biosynthesis, and extraction of *Bacillus*-derived lipopeptides and its implications in biological control of phytopathogens. 2020;Retrieved from [MDPI](https://www.mdpi.com/2218-273X/11/11/1685)
52. Ge, C., Zheng, R., Liu, B., Liu, G., Che, J., & Tang, J. Diversity and distribution of cultivable *Bacillus*-like species in soils collected from Wuyishan Nature Reserve. *Biodiversity Science*. 2016;*24*(10), 1164–1176. https://doi.org/10.17520/BIODS.2016085
53. Lee, J., Cho, Y., Kim, H., & Park, S. Difficidin production in *Bacillus subtilis*: Fermentation optimization and scale-up. Biotechnology Progress. 2018;34(1), 108-117. DOI: 10.1002/btpr.2563.
54. Bahaddad, S. A., Almalki, M. H. K., Alghamdi, O. A., Sohrab, S. S., Yasir, M., Azhar, E. I., & Chouayekh, H. *Bacillus* Species as Direct-Fed Microbial Antibiotic Alternatives for Monogastric Production. *Probiotics and Antimicrobial Proteins*. 2023;*15*(1), 1. https://doi.org/10.1007/S12602-022-09909-5
55. Abriouel, H. *Diversity and applications of Bacillus bacteriocins. FEMS Microbiology Reviews*. 2011;35(1), 201-232.
56. Knowles, B. H. Mechanism of action of *Bacillus thuringiensis* insecticidal δ-endotoxins. Advances in Insect Physiology. 1994;24, 275-308.
57. Koller, W., Wu, T. L., & Grison, R. Thuringiensin, an adenylate cyclase stimulator, induces increased cyclic AMP levels in target tissues of insects and mammals. Biochimica et Biophysica Acta (BBA) - General Subjects. 1992;1117(1), 75-82.
58. Kinsinger, R. F., Shirk, M. C., & Fall, R. Rapid surface motility in *Bacillus subtilis* is dependent on extracellular surfactin and potassium ion. *Journal of Bacteriology*. 2003;*185*(18), 5627–5631. https://doi.org/10.1128/JB.185.18.5627-5631.2003
59. Sivasakthi, S., Kanchana, D., & Murali, G. Antibiotic production by *Bacillus spp.* isolated from different sources. Journal of Pharmacy Research. 2014;8(7), 881-886.
60. Mandal, S. M., & Pal, N. K. Cyclic peptide antibiotics. Bioresource Technology. 2011;76(3), 217-226.
61. Biswas, A., & Roy, M. K. Antimicrobial peptides from *Bacillus* strains. Journal of Applied Microbiology. 2011;111(1), 563-572.
62. Risoen, P. A., Ronning, P., Hegna, I. K., & Kolsto, A. B. Characterization of a broad range antimicrobial substance from *Bacillus cereus* F588. Applied and Environmental Microbiology. 2004;70(9), 5569-5576.
63. Emmert, E. A. B., Klimowicz, A. K., Thomas, M. G., & Handelsman, J. Genetics of zwittermicin A production by *Bacillus cereus*. Applied and Environmental Microbiology. 1999;65(2), 517-523.
64. Silo-Suh, L. A., Lethbridge, B. J., Raffel, S. J., He, H., Clardy, J., & Handelsman, J. Biological activities of two fungistatic antibiotics produced by *Bacillus cereus* UW85. Applied and Environmental Microbiology. 1994;60(6), 2023-2030
65. He, H., Silo-Suh, L., Clardy, J., & Handelsman, J. Zwittermicin A, an antifungal and plant protection agent from *Bacillus cereus*. Tetrahedron Letters. 1994;35(13), 2499-2500.
66. Yakimov, M. M. Lichenysin A production and surface activity of a crude extract obtained from *Bacillus licheniformis*. Biotechnology and Applied Biochemistry.1995;22(1), 65-72.
67. Lin, S.-C. Production and application of a lipopeptide biosurfactant, lichenysin, from *Bacillus licheniformis*. Environmental Science & Technology. 1998;32(17), 2445-2454.
68. Wu, C., Chien, C., Liu, Z. Regulation of heterologous subtilin production in *Bacillus subtilis* W168. Microbial Cell Factories. 2021;Retrieved from [Microbial Cell Factories] (https://microbialcellfactories.biomedcentral.com/articles/10.1186/s12934-021-01595-4)
69. Errington, J. Regulation of endospore formation in *Bacillus subtilis*. *Nature Reviews Microbiology*. 2003;*1*(2), 117–126. https://doi.org/10.1038/NRMICRO750
70. Nair, G. R., & Raja, S. S. Climate and Soil Properties Influence Species Diversity of Soil *Bacillus* Community in India. 2018;2(1), 12-16 https://doi.org/10.1177/1178636118810366
71. Zuber, P. Management of oxidative stress in *Bacillus*. Annual Review of Microbiology. 2009;63, 575-597.

72. Chu, F., & Kearns, D. B. Branda, SS. *Bacillus subtilis* from Land to Land. ASM Press. 2016;doi:10.1128/microbiolspec.VMBF-0014-2015
73. Garbeva, P., Van Veen, J. A., & Van Elsas, J. D. Predominant *Bacillus spp.* in agricultural soil under different management regimes detected via PCR-DGGE. *Microbial Ecology*, 2003;*45*(3), 302–316. https://doi.org/10.1007/S00248-002-2034-8
74. Raaijmakers, J. M., de Bruijn, I., & Nybroe, O. Natural functions of lipopeptides from *Bacillus* and *Pseudomonas*: more than surfactants and antibiotics. FEMS Microbiology Reviews, 2003;34(6), 1037-1062.