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Dipeptide and Cyclic-peptide Secondary Metabolites Derived from *Streptomyces*: Molecular Structure and Therapeutic Applications

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Abstract

Purpose: In this review, we focus specifically on dipeptides and cyclic dipeptides derived from *Streptomyces*, exploring their structural diversity, biosynthesis pathways, and potential therapeutic applic-ations. This subject only gathers information about dipeptide and cyclic peptide however most review paper in *Bacillus* are about lipopeptide which has lipid domain

Methods: This review is prepared with collection of many literatures about antimicrobial peptides from *Streptomyces*. The most data were used from PDB with dipeptide and cyclic peptide in *Streptomyces* and the formula obtained from Chemical ACTA

Results: *Streptomyces* are prolific producers of secondary metabolites and antibiotics, contributing significantly to pharma-cology and industry fields. They are widely distributed in various environments. These gram-positive strains are generally non-pathogenic. There are only a few *Streptomyces* species (like *Strep-tomyces somalensis* and *Streptomyces sudanensis*, which cause endemic actinomycetoma) that are pathogenic under certain con-ditions. While many antibiotics originate from *Streptomyces*, ongoing research continues to unveil novel metabolites with diverse biological activities, including anticancer, antibacterial properties, and others whose functions remain undiscovered. Some of these peptides like albonoursin and alahopsin are self-assembled dipeptides.

Conclusion: Application, design and engineering of dipeptides and cyclic dipeptides from *Streptomyces* could be a novel method in development of therapeutic purposes, especially for reduction of human toxicity.

***Keywords*:** Antibacterial, Antimicrobial peptides, dipeptides, Cyclic peptide, *Streptomyces*

What is "already known":	The artificial dipeptide and dipeptide self-assemble are reported for application in drug delivery and cancer treatment. Bacterial self-assemble dipeptides reports are rare.
What this article adds:	This review give most dipeptide metabolite which has taken from protein data bank (PDB) to introduces bacterial dipeptide. Some of dipeptide metabolite have self-assemble capacity and have potential for virus and bacterial infection treatments A few of dipeptide metabolite are a good natural treatment for cancer therapy.

1. Introduction

Antimicrobial peptides (AMPs) are one of the diverse groups of antimicrobial substances that have been interested due to the development of resistance of pathogenic bacteria to common antibiotics. These protein-like molecules often contain altered and modified amino acids that are not found in polypeptides made by ribosomes. These compounds include two groups of peptide antibiotics and bacteriocins, which are based on their biosynthesis mechanism. Bacteriocins are compounds synthesized by ribosomes that are produced in bacteria and are active against other bacteria that are closely related to the producing strains. Antibiotic peptides are not synthesized by ribosomes and instead are made during complex stepwise compression reactions that utilize large non-ribosomal peptide synthetases (NRPS). The main problem in using AMPs as antibiotics is their killing effect on eukaryotic cells. To use them as medicinal agents, they should have low hemolytic activity with high antimicrobial activity. Other challenges such as toxicity, low bioavailability, and high manufacturing cost, should also be considered. Several host-vector systems have been used to produce AMPs using recombinant DNA technology, among them *Escherichia coli* has been used the most. Therefore, there is a high potential in the field of using antimicrobial peptides, and further research in this field could potentially lead to significant effects in the medical and food industries [1]. Among the useful microorganisms used to control fungal diseases, *Bacillus* species have been considered due to having strong antagonistic activity, a wide range of inhibitory activity, and high viability [2]. *Bacillus* species are widely able to produce metabolites with antagonistic activity to perform their biological control function, which includes lipopeptide antibiotics, secreted proteins with antifungal activity, and volatilecompounds with low molecular weight. This species plays a role in biotechnology as a source of limited endonucleases [3]. Antimicrobial cyclic peptides derived from different species of*Bacillus* are classified into three main families based on amino acid sequence and fatty acid branching: i) iturins ii) fungicins and iii) surfactins [4]. Iturins family are beta-amino fatty acid heptapeptides with great antifungal activity. Cyclic lipopeptides include iturins A/C/E/D, bacillomycins D/F/L/LC, and mycosubtilins [5]. The cyclic structure in the iturin family includes the COOH-7 agent - serine and NH2 agent - beta-amino fatty acid chains. The ability to penetrate the membrane is the factor of the antifungal activity of iturins. *Streptomyces* are the source of many of the world's antibiotics and represent a very important bacterial genus. They are present in almost all environments from high mountains to deep sea. They are spore-forming gram-positive bacteria that are members of the phylum Actinobacteria. *Streptomyces* are non-motile bacteria that spread by constructing narrow hyphae that penetrate surfaces to get nutrients. When foods are limited, *Streptomyces*produce aerial hyphae and spores that can resist uncomplimentary conditions andare easily spread to new environments to get nutrition. *Streptomyces* produce secondary metabolites: compounds that give the organism a competitive advantage and are not strictly necessary for growth or reproduction. These metabolites help the vegetative bacterial cells by inhibiting competitors (antibiotics), repossessing metals such as iron (siderophores), protecting them from UV light (pigmentation), and also helping communication with other species. This molecular diversity is possible in *Streptomyces* due to their relatively large genome, compared to other bacterial genomes [6].

In comparison with other bacteria, Actinobacteria produce natural peptide products with complex structures which contributes to the research for the

discovery of novel antibiotics. Actinobacteria produce many peptides that are classified into eight different classes: lipopeptides (peptides with linear or cyclic structures having an aromatic acid hydrocarbon tail or lipophilic fatty acid that are linked to the N-terminal of a short oligopeptide), 2,5-diketo-piperazines (DKPs are important cyclodipeptides derived from the "head to tail" cyclization of two -amino acids), dimeric peptides (two typical cyclic peptides by polymerization constitute dimeric peptides), nucleosidyl peptides (deoxyuridine is linked to the third amino acid), thioamide-containing peptides, thiopeptides (thiazolyl, or thiopeptides peptides, are highly modified sulfur-rich peptides of ribosomal origin), lasso peptides or lariat peptides (The ribosomally synthesized and post-translationally modified peptides), and typical cyclic peptides [7].

Self-assembled dipeptides are modified that cross-linked by three-dimensional networks and hold a large amount of water. By definition, water should constitute at least 10% of the total weight (or volume) in peptide hydrogels. Some features of hydrogels such as the high water content, favorable structure, and biocompatibility, make them a good candidate for biomedical applications such as sensing drug delivery, cell culture scaffolds, and tissue engineering [8]. Hydrogels are classified into chemical and physical hydrogels, based on the different gelation mechanisms. They cross-linked via covalent bonds, causing structural stability, high mechanical strength, irreversible properties, and shape memory [9].

This review shows dipeptides and cyclic dipeptides from *Streptomyces*, their molecular structure, and many other features. Also, developments in these metabolites to enhance their positive effects and reduce their human toxicity are mentioned.

2. Self-assembly dipeptide and cyclic peptide hydrogel

Self-assembly peptide hydrogels are produced and synthetized since have applications in biomedical since the fact that they are easy to design, manageable, and have bio-compatibility properties. A dipeptide, the shortest self-assembling motif of peptides, can provide a simple and easy-to-use method for studying the self-assembly mechanism in peptides, due to its small size and simple synthesis method [9] Dimeric peptides are less studied compound from *actinomycete*s, however, albonoursin and alahopsin are self-assembled dipeptides but in this paper, we focused on the production of dipeptides from *streptomyces sp*. Some compound like Nocardamine, also called desferri-oxamine, is a cyclic peptide siderophore found in several species of bacteria, *including Nocardia, Pseu-domonas*, and *Streptomyces*. This cyclic peptide is an excellent candidate for mycobacterial disease therapy

3. Actinobacteria

This group includes mostly non-pathogenic bacteria found in water, soil, and nature such as Actinomycetes, Streptomyces, and Nocardia. Some of them like actin-omycetes, are very alike to fungi, but the absence of a nucleus and the peptidoglycan compounds in cell wall confirm that they are prokaryotes. This category can be classified in different ways, including dividing it into the following five orders:

- Actinomycetidae e.g. Bifidobacteriales, Actino-mycetales and Actinomycetes
- Acidimicrobiidae such as Acidimicrobiales
- Coriobacteriaidae such as Coriobacteriales
- Nitriliruptoridae such as Nitriliruptorales
- Rubrobacteridae e.g. Rubrobacterales

Actinobacteria are a group of Gram-positive bacteria with high (G+C) DNA content. Actinobacteria are distributed in many habitats including marine, aquatic, terrestrial, and extreme environments like polar region deserts and acid mines. Some have symbiotic life with animals, sponges, fishes, and

plants [10]. Actinobacterial genera have aerobic mycelium and replicate by binary fission or spore formation. While the substrate mycelium differs in size, shape, and thickness with colors ranging from white to yellow, red, brown, orange, pink, black, or green, the aerial mycelium is thicker than substrate mycelium, differs in the ring formation/concentric zones, color, andstructure (cotton, velvet, or powder). Primary characteristics for the recognition of actinobacterial included: the development of aerial mycelium and its color, elongation and branching of mycelium, and spore germination. The formation of substrate and aerial mycelium can be observed with light microscopy whereas the surface and structure of spores are studied under scanning electron microscopy [11]. The Actinobacterial genera are often mesophilic in nature. However, the thermophilic and psychrophilic forms can grow at 55–60°C and 4°C, respectively [12]. Cellulose and chitin decomposition are important functions of actinobacteria, however, many secondary metabolites and antibiotics are produced by actinobacteria in concern with pharmacology and industry.

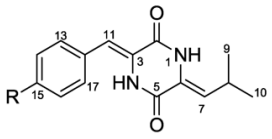
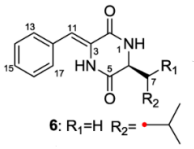
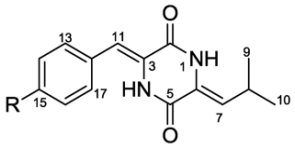
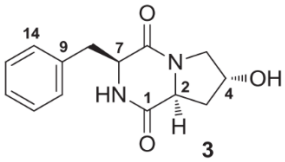
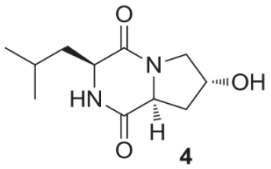
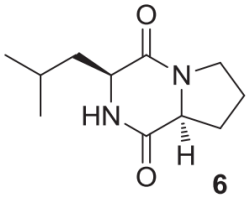
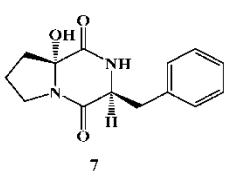
4. 2,5-diketopiperazines (DKPs)

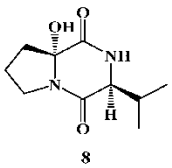
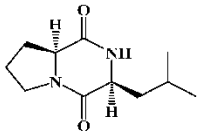
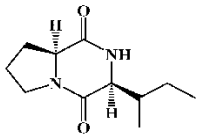
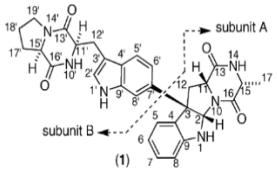
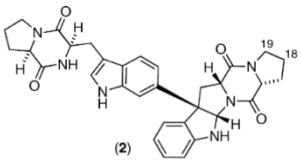
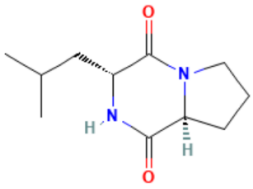
DKPs are cyclodipeptides resulting from the "tail to head" cyclization of two amino acids. These peptides are naturally unwanted by-products produced by fungi (like cyclo Pro-Val from *Aspergillus* (*A.*) *fumigatus*, cyclo- Ala-Leu from *A. niger*), Actinomycetes (like cyclo serine dimer) and *Streptomycetes* (Amphomycin & Albon-oursin dimeric peptides). These compounds are often neutral, nonionic in water and have the ability to form hydrogen bonds with solvents. These compounds have antibacterial, antiviral, anticancer, and antifungal activities. DKPs are more stable comparedto linear dipeptides due to the lack of free amine or acid terminal and most are stable at pH= 4.6-7. Table 1 shows DKPs are produced by *Streptomyces*.

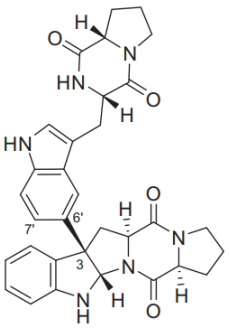
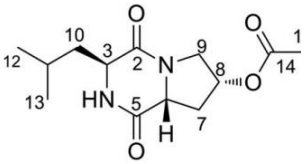
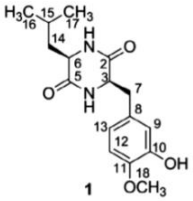
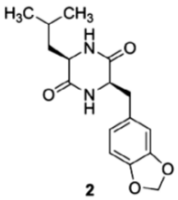
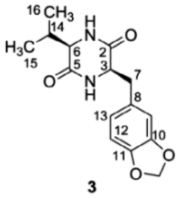
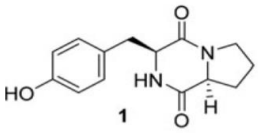
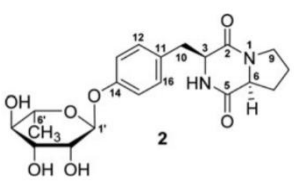
5. Fermentation and production

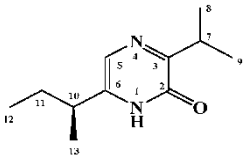
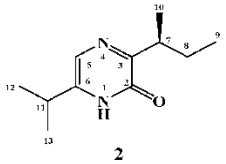
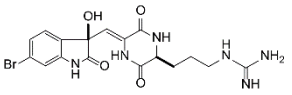
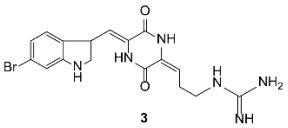
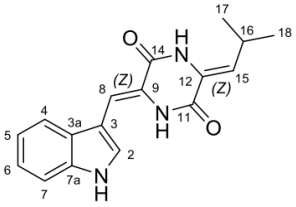
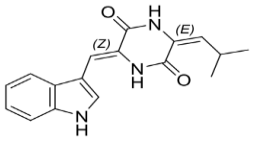
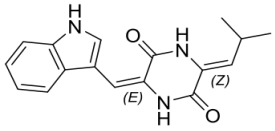
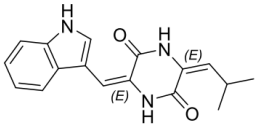
Diverse methodologies were implemented to cultivate and isolate bioactive compounds of bacterial origin within the scope of this investigation. For instance, in the study by Wang et al [13] *Streptomyces* spores were subjected to direct culturing at a neutral pH of 7 and maintained at 28°C with agitation at 180 rpm for an incubation period of 8 days, followed by extraction using ethyl acetate (EtOAc) as the . solvent, yielding a viscous dark brown resin [13] On the other hand, similar strains of *Streptomyces* underwent identical culturing and extraction regimens [14]. For some of the bacterial strains, a protocol involving initial cultivation at pH 8 and 28°C under agitation for 4 days, followed by transfer to a liquid medium and subsequent incubation for 14 days under congruent conditions [15-17]. Fermentation of bacterial species in marine broth afforded compounds extractable with EtOAc, subsequently subjected to reverse-phase HPLC, culminating in the isolation of dimeric diketopiperazines [14, 18-20]. Moreover, some bacterial strains that needed to be cultured on marine agar were extracted with EtOAc, and the resultant extracts were partitioned and subjected to reversed-phase column chromatography to yield discernible fractions [16,21]. Bacteria isolated from marine sediments were cultivated on CYC agar, followed by extraction with ethyl acetate and purification by HPLC[19] Variability in culturing methods was observed, including spore-based propagation [13,14,22] the establishment of pure colonies [23] and initial cultivation in seawater-based media [17] each followed by tailored extraction and purification methodol-ogies to suit the unique characteristics of the bacterial strains under investigation.

Table 1. 2,5-diketopiperazines (DKPs) derived from *Streptomyces* .They are more rigid and stable than linear peptides, often showing high resistance to breakdown by enzymes.

Number	Name	Strain	Structure	Activities	Molecular weight	Reference
1	(3Z,6Z)-3-(4-hydroxybenzylidene)-6-isobutylidenepiperazine-2,5-dione	Marine-derived Actinomycete *Streptomyces* sp. FXJ7.328	 **3**: R=OH; **7**: R=H	Antiviral H1N1	273.1234	13
2	(3Z,6S)-3-benzylidene-6-(2S-but-2-yl)piperazine-2,5-dione	Marine-derived Actinomycete *Streptomyces* sp. FXJ7.328	 **6**: R_1=H R_2=	Antiviral H1N1		13
3	Albonoursin	Marine-derived Actinomycete *Streptomyces* sp. FXJ7.328	 **3**: R=OH; **7**: R=H	Antiviral H1N1	256.30	13
4	Cyclo-(l-phenylalanine-l-4-hydroxyproline)	*Streptomyces* sp. Q24	 **3**	Inhibits the proliferation of human glioma U87-MG and U251 cells	260.288	15
5	Cyclo-(l-leucine-l-4-hydroxyproline)	*Streptomyces* sp. Q24	 **4**	Inhibits the proliferation of human glioma U87-MG and U251 cells	226.27	15
6	Cyclo-(l-leucine-l-proline)	*Streptomyces* sp. Q24	 **6**	Inhibits the proliferation of human glioma U87-MG and U251 cells	210.27	15
7	Cyclo(6-OH-d-Pro-l-Phe)	A tunicate-derived Actinomycete, *Streptomyces* sp.. 98% similarity with type strains of *Streptomyces flocculus* (DQ442498) and *Streptomyces*	 **7**	Moderately active against MCF-7 and weakly active against HepG2 cell line.	?	14

		rangoonensis (NR_041110).				
8	Bacillusamide B	Same as number 7	 8	Moderately active against MCF-7 and weakly active against HepG2 cell line.	212.25	14
9	Cyclo(l-Pro-l-Leu)	Same as number 7	 9	Moderately active against MCF-7 and weakly active against HepG2 cell line.	210.27	14
10	Cyclo(l-Pro-l-Ile)	Same as number 7	 10	Moderately active against MCF-7 and weakly active against HepG2 cell line.	210.27	14
11	Naseseazine A	*Streptomyces* sp. (CMB-MQ030) isolated from a Fijian marine sediments	 (1)	Not toxic, probable role in immunosuppressants, pain relief, hypertension	538.6	18
12	Naseseazine B	*Streptomyces sp.* (CMB-MQ030) isolated from a Fijian marine sediments	 (2)	Not toxic, probable role in immunosuppressants, pain relief, hypertension	564.6	18
13	Cyclo-(L-proline-L-leucine)	*Streptomyces gougerotii GT*		Significant reduction effect on the dengue virus type 2 replication	210.27	16

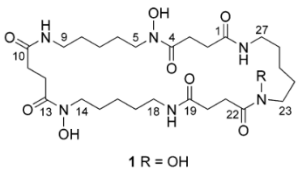
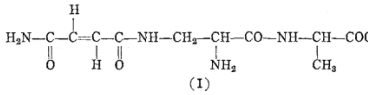
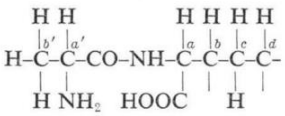
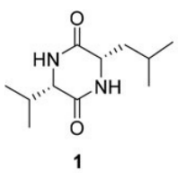
14	Naseseazine C	The *Streptomyces sp* Accession Number KX379154) was isolated from marine sediment obtained on the Sunshine Coast, QLD, Australia.	 5	Moderate activity against the chloroquine-sensitive malaria parasite, Plasmodium falciparum (3D7 strain)	564.6	19
15	Cyclo-(D-8-acetoxyl-Pro-L-Leu)	*Streptomyces sp.* SCSIO 41,400 was isolated from the mangrove soil,		Treatment against obesity	269.1496	24
16	3-(3-hydroxy-4-methoxybenzyl)-6-isobutyl-2,5-diketopiperazine	*Streptomyces sp. MNU FJ-36* isolated from *Katsuwonus* sp. Intestine	 1	Weak inhibition against A549 (human lung adenocarcinoma)	306.36	21
17	3-(1,3-benzodioxol-5-ylmethyl)-6-isobutyl-2,5-diketopiperazine	*Streptomyces sp. MNU FJ-36* isolated from *Katsuwonus* sp. Intestine	 2	Weak inhibition against A549 (human lung adenocarcinoma) and HCT-116 (human colon carcinoma)	?	21
18	3-(1,3-benzodioxol-5-ylmethyl)-6-isopropyl-2,5-diketopiperazine	*Streptomyces sp. MNU FJ-36* isolated from *Katsuwonus* sp. Intestine	 3	Weak inhibition against A549 (human lung adenocarcinoma) and HCT-116 (human colon carcinoma)	?	21
19	Maculosin (L-Pro-L-Tyr)	*Streptomyces sp. ZZ446.*	 1	Antimicrobial activity against MRSA, *E. coli*, and *Candida albicans*	260.29	20
20	maculosin-O-a-L-rhamnopyranoside	*Streptomyces sp. ZZ446.*	 2	Antimicrobial activity against MRSA, *E. coli*, and *C. albicans*	407.182	20

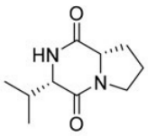
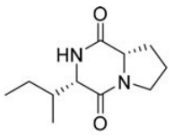
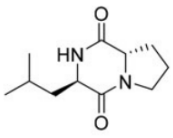
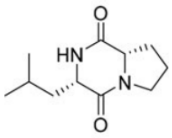
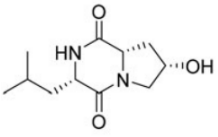
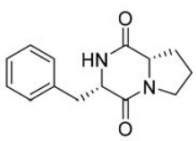
21	Actinozine A	*Streptomyces sp. Call-36*		Potent activity against *Staphylococcus aureus* and were moderately active against *C. albicans*	243.1345	22
22	Cyclo(2-OH-d-Pro-l-Leu)	*Streptomyces sp. Call-36*	 2	Potent activity against *S. aureus* and were moderately active against *C. albicans*	227.1396	22
23	Streptodiketopiperazines A	*Streptomyces sp. SY1965* was collected from the Mariana Trench sediment-associated at a depth of 11,000 m		Weak antifungal activity against *C. albicans*	231.1134	23
24	Streptodiketopiperazines B	*Streptomyces sp. SY1965* was collected from the Mariana Trench sediment-associated at a depth of 11,000 m	 3	Weak antifungal activity against *C. albicans*	231.1134	23
25	Photopiperazine A	*Strain AJS-327* was isolated from a detached sponge fragment (unidentified) a novel lineage, likely a new genus within the Actinomycete family Streptomycetaceae		Potent and selective growth inhibition of human U87 glioblastoma brain cancer and SKOV3 ovarian cancer cell lines, breast cancer and HCT116 human colon carcinoma	296.1399	17
26	Photopiperazine B	Same as number 25		Same as number 25	296.1399	17
27	Photopiperazine C	Same as number 25		Same as number 25	Not purified	17
28	Photopiperazine D	Same as number 25		Same as number 25	Not purified	17

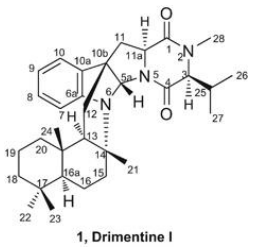
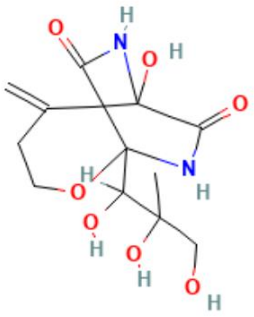
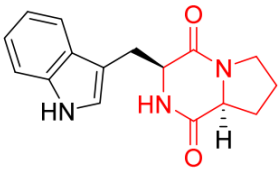
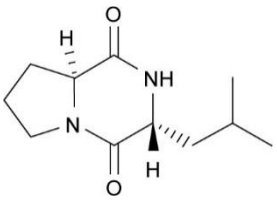
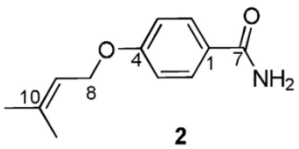
6. Dipeptides and cyclic-dipeptides from *Streptomyces*

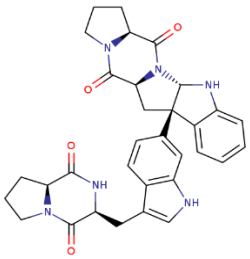
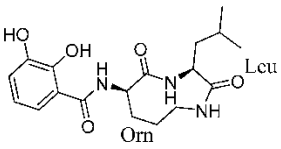
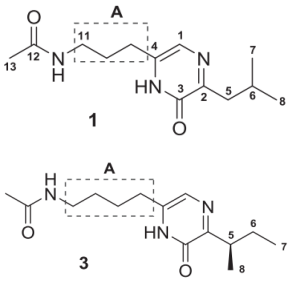
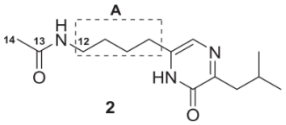
There are many other dipeptides and cyclic-dipeptides produced by *Streptomyces* (table 2). It is noteworthy that the majority of these compounds exhibit stability under neutral conditions, with a few exceptions. Notably, dipeptides number 2, 3, 12, and 13 in table 2 have demonstrated activity under alkaline conditions as well. Current literature indicates that among these, fumaryl carboxyamido-L-2,3-diamino propionyl-L-alanine stands out as the sole compound displaying activity across both acidic and alkaline environments.

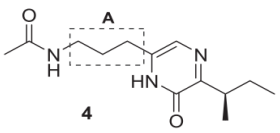
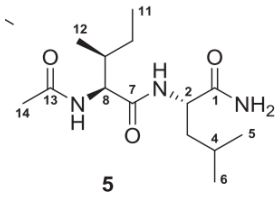
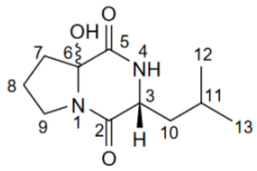
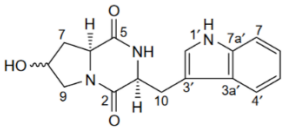
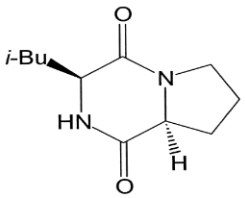
Table 2. Other Dipeptides and cyclic-peptides derived from *Streptomyces*, with their structures, activities, and molecular weight.

Number	Name	Strain	Structure	Activities	Molecular weight	Reference
1	Nocardamine	*Streptomyces* isolated from an unidentified marine sponge (*Streptomyces hygroscopicus* var. *geldanus*)	 1 R = OH	Antibacterial activity against Mycobacteria	601.3564	25-27
2	Fumaryl carboxyamido-L-2,3-diamino propionyl-L-alanine	*Streptomyces collinus*	 (I)	Antibacterial activity against *salmonella gallinarum*	272.26	28
3	Alahopcin	*Streptomyces albulus*		Against Gram+ and gram – specially *S. aureus*, against a pathogenic fungus, *Sclerotinia sclerotiorum*	279.25	3,29
4	Cyclo-(L-Val-L-Leu)	*Streptomyces xiamenensis* MCCC 1A0157	 1	Mild cytotoxicity against ECA-109, Hela-S3 and PANC-1 cancer cell lines	212.29	30

5	Cyclo-(L-Pro-L-Val)	*Streptomyces xiamenensis* MCCC 1A0157	 2	Mild cytotoxicity against ECA-109, Hela-S3 and PANC-1 cancer cell lines	196.25	[30,31]
6	Cyclo-(L-Ile-L-Pro)	*Streptomyces xiamenensis* MCCC 1A0157	 3	Mild cytotoxicity against ECA-109, Hela-S3 and PANC-1 cancer cell lines	210.27	[30]
7	Cyclo-(L-Pro-D-Leu)	*Streptomyces xiamenensis MCCC 1A0157*	 4	Mild cytotoxicity against ECA-109, Hela-S3 and PANC-1 cancer cell lines	210.27	[30,32]
8	Cyclo-(L-Pro-L-Leu)	*Streptomyces xiamenensis* MCCC 1A0157	 5	Mild cytotoxicity against ECA-109, Hela-S3 and PANC-1 cancer cell lines	210.27	[30,33]
9	Cyclo-[L-(4-hydroxyprolinyl)-L-isoleucine]	*Streptomyces xiamenensis MCCC 1A0157*	 6	Mild cytotoxicity against ECA-109, Hela-S3 and PANC-1 cancer cell lines		[30]
10	Cyclo-(L-Pro-L-Phe)	*Streptomyces xiamenensis* MCCC 1A0157	 8	Mild cytotoxicity against ECA-109, Hela-S3 and PANC-1 cancer cell lines	244.29	[30,34,35]

11	Drimentine I	*Streptomyces* sp. CHQ-64	 1, Drimentine I	Weak activity against human cervical carcinoma cell line HeLa.	503.7	36
12	Bicyclomycine	*Streptomyces sapporonensis* ATGG 21532, i And *Streptomyces aizunensis*		Antidiarrheal, against gram-negative bacteria such as *E. coli, Klebsiella, Salmonella, Shigella, Citrobacter, Enterobacter*	302.28	37-39
13	Brevianamide F, cyclo(L-Trp-L-Pro)	*Streptomyces* sp. strain TN58		Against *Micrococcus luteus S. aureus*	283	31,40-42
14	Gancidin W	The endophytic actinobacterial genus *Streptomyces*, SUK10, obtained from the bark of *Shorea ovalis* tree		Antimalarial activity against *Plasmodium berghei* PZZ1/100 strain	210.275	43-46
15	Cyclo-(L-Val-L-Pro)	*Streptomyces spectabilis HDa1* was isolated from the sea urchin *Anthocidaris crassispina*.	 2	Natural AChE inhibitors that may provide a new chance for drug development for the treatment of neural	197.1285	47

				degeneration disease.		
16	Iso-naseseazine B	*Streptomyces sp.* SMA-1 from the marine sediment of the Yellow Sea, China. 99.92 % 16S rDNA similarity with the closest relative *S. cacaoi subsp. cacaoi* NBRC 12748T		Oppose the fluconazole-resistant *C. albicans* and no antibacterial activity	564.646	[48]
17	Petrocidin A	*Streptomyces sp.* SBT348 (GenBank accession No. KP238417) cultivated from Mediterranesponge *Petrosia ficiformis* that was collected from Milos, Greece		Cytotoxicity against HL-60 and HT-29 cancer cell lines	383.1691	[49]
18	Streptopyrazinone A (transformed dipeptide)	*Streptomyces sp. ZZ446* s isolated from a sample of coastal soil, which was collected from Zhoushan Islands (Zhejiang, China) in August 2016.		Inhibiting the growth of *C. albicans* and MRSA	252.1712	[50]
19	Streptopyrazinone B (transformed dipeptide)	*Streptomyces sp.* ZZ446.		Inhibiting the growth of *C. albicans* and MRSA	266.1869	[50]
20	Streptopyrazinone C (transformed dipeptide)	*Streptomyces sp. ZZ446*.		Inhibiting the growth of *C.*	266.1869	[50]

				albicans and MRSA		
21	Streptopyrazinone D (transformed dipeptide)	*Streptomyces* sp. ZZ446.	 4	Inhibiting the growth of *C. albicans* and MRSA	252.1708	50
22	N-acetyl-L-isoleucine-L-leucinamide	*Streptomyces sp. ZZ446*	 5	Inhibiting the growth of *C. albicans* and MRSA	286.2131	50
23	Cyclo(2-hydroxy-Pro-R-Leu)	*Streptomyces sp.* MS-2. Actinomycete strain, WuXin, isolated from marine sediment at intertidal zone of Bohai Bay of China in Aug2008.		Moderate cytotoxic activities against HL-60	249.1210	51
24	Cyclo(4-hydroxy-S-Pro-S-Trp)	*Streptomyces sp.* MS-2. Actino-mycete strain, WuXin,		Inhibiting growth of *C. albicans* & MRSA	220.22	51
25	Cyclo(L-leucyl-L-prolyl)	Actinomycete strain KH-614, a member of *Streptomyces lydicus*		Active against 12 VRE† e.g. *E. faecium* (vanA, vanB), & *E. faecalis* (vanA, van B), *E. faecalis* (K-99-34), (K-00-184), (K-00-221). Against 3 leukemic cell, K562, HL60, and U937.		52

†vancomycin-resistance enterococci

6.1. Newly studied dipeptides and cyclic-dipeptides from *Streptomyces*

Cyclo-(L-Val-L-Leu): Cyclo- (L-Val-L-Leu) is a neutral cyclic dipeptide, with a molecular weight of 212.29 Da, which is produced by microorganisms such as *Streptomyces xiamenensis* MCCC 1A0157 [30] endophyte fungus *Fusarium* sp. LC-1 [53] and *Bacillus subtilis* C-3102 [54] This peptide has various properties, including a selective anticancer effect against Hela-S3 and PANC-1 cancer cells with an inhibition rate of around 50% [30] and stimulating the growth of *Bifidobacterium* strains, without stimulating the growth of harmful bacteria in the gut.[54] Since Bifidobacteria are probiotic members of the gut microbiome, stimulating their growth can be beneficial for digestive health. The mentioned anticancer and stimulating effects can make this cyclic dipeptide a suitable candidate for use as medicine.

Cyclo-(L-Pro-L-Val): This cyclic-dipeptide with a formal charge of 0 and 196.25 Da molecular weight, is produced by *Streptomyces xiamenensis* MCCC 1A0157 [30] *A. fumigatus [*31] symbiotic marine bacterium *Micrococcus* sp., and *Vibrio parahaemolyticus* isolated from the toxic mucus of the box fish *Ostracion cubicus* [55]. It has mild cytotoxicity against ECA-109 cancer cell lines [30] and weak antibacterial activity against *Staphylococcus aureus* and *Micrococcus luteus* [31]. Also, this cyclic-dipeptide has effects on bacterial quorum sensing-dependent phenotypes: it activates violacein pigment production in the *Chromobacterium violaceum* AHL reporter strain CV026 and inhibits quorum sensing dependent phenotypes in *E. coli* JM109(pSB401) [56] Quorum sensing is one of the most important systems in virulence factors controlling, so inhibition of pathogenic bacteria by quorum quenching is a new method [57]. This cyclic-dipeptide with multi-functional advantages such as anti-cancerous and quorum quenching effects could be useful for therapeutic purposes.

Cyclo-(L-Ile–L-Pro): This 210.27 Da cyclic-dipeptide with no charge, has mild cytotoxicity against ECA-109 cancer cell lines [30] and nematode mortality with a rate of 46.19 %.[58] Cyclo-(L-Ile-L-Pro) is produced by *Streptomyces xiamenensis* MCCC 1A0157 [30] and *Pseudomonas putida* MCCC 1A00316 [58]

Cyclo-(L-Pro-D-Leu): This cyclic dipeptide is an uncharged peptide with 210.27 Da molecular weight, which is produced by *Streptomyces xiamenensis* MCCC 1A0157,[30] and *Bacillus cereus* subsp. *thurigenesis* (Accession No. CP001407) [32] Cyclo-(L-Pro-D-Leu) has a selective effect against Hela-S3 and PANC-1 cancer cells with an inhibition rate of around 50%.[30] Additionally, it has antifungal effect against *A. flavus* by inhibiting mycelia growth of fungus and thereby affecting aflatoxin production, which is useful for reducing mycotoxin formation in the food industry [32]

Cyclo-(L-Pro-L-Leu): This cyclic-dipeptide has no charge with 210.27 Da molecular weight. It is produced by some microorganisms such as *Streptomyces xiamenensis* MCCC 1A01570 [30] *Streptomyces misionensis* V16R3Y1 (10), and *Pseudomonas putida* MCCC 1A00316 [58] This dipeptide is a broad spectrum inhibitor against cancer cell lines, gram-positive and gram-negative bacteria, and fungi. For example, it has a mild effect against ECA-109 cancer cell lines [30] as well as a significant inhibitory effect against *Fusarium oxysporum, A. flavus, A. niger, Penicillium expansum, Candida albicans, Candida metapsilosis,* and *Candida parapsilosis*. Among gram-negative bacteria, *Escherichia fergusonii* and *Salmonella enterica* showed the highest and lowest resistance, respectively. Among gram-positive bacteria, *Enterococcus faecalis* was found to be the

most sensitive to this cyclic dipeptide.[32] Furthermore, this dipeptide has a nematicidal activity against *Meloidogyne incognita* [58] This broad-spectrum activity makes it a good candidate for therapeutic purposes.

Cyclo-[L-(4-hydroxyprolinyl)-L-isoleucine]: This cyclic dipeptide that is produced by *Streptomyces xiamenensis* MCCC 1A0157 [30] *Microbacterium* sp. MCCC 1A11207 [59] and a bacterial strain A108, isolated from *Palyrhoa* sp. [60] has mild cytotoxicity against ECA-109 cancer cell lines [30] It is also isolated from animal skin tissue probably as a metabolite of collagen, which possessed the effect as a rice germination promoter [61]

Cyclo-(L-Pro-L-Phe): This cyclic-dipeptide with no charge and a molecular weight of 244.29 Da, is produced by *Streptomyces xiamenensis* MCCC 1A0157 [30] *Pseudomonas fluorescens* strain isolated from rhizosphere of groundnut crop [34] and *Bacillus sp*. N strain associated with *rhabitid entomopathogenic* nematode [35]. It has a selective effect against Hela-S3 and PANC-1 cancer cells with an inhibition rate of around 50% [30]. This cyclic-dipeptide has antifungal effects against a sorghum grain mold fungus [34]. *Fusarium oxysporum, Rhizo-ctonia solani,* and *Pencillium expansum* [35].

Brevianamide F, cyclo(L-Trp-L-Pro): This cyclic-dipeptide is a 283 Da dipeptide with no charge and probably is alkaline. It is produced by *Streptomyces* sp. TN58 [40] *Streptomyces* sp. TN262 [62] marine fungi *A. fumigatus* and *Aspergillus sp* [31] and other *Streptomyces* spp. It has anticancer activity against HCT-116 cancer cells [63] antibacterial activity against *Staphylococcus aureus* ATCC 6538 and *Microco-ccus luteus* LB 14110 [40] and antifungal activity [42]. This cyclic dipeptide is a valuable candidate for therapeutic purposes, due to its broad-spectrum activity against cancer cells, bacteria, and fungi.

Gancidin W: This netral cyclic dipeptide with 210.275 Da molecular weight, is produced by the endophytic actinobacterial genus *Streptomyces*, SUK10, obtained from the bark of *Shorea ovalis* tree [43] endophytic fungal strain *Acremonium* sp. Ld-03 [46] and other actinomycetes [45] This multifunctional cyclic-dipeptide has an anti-malarial effect against *Plasmodium berghei* PZZ1/100 with very low toxicity in an animal model [43] antitumor [44] antibacterial, anti-fungal, and antiviral activities [46]. Its low toxicity makes it a good candidate for use as medicine.

Cyclo-(D-8-acetoxyl-Pro-L-Leu): This cyclic dipeptide with pH 7 and 269 Da molecular weight is obtained from the fermentation extract of *Streptomyces* sp. SCSIO 41,400 was isolated from the mangrove soil, which was collected from the Fuli Mangrove Bay Wetland Park, Haikou, Hainan Province of China. It shows preferable pancreatic lipase enzyme inhibition activity, which is confirmed by molecular docking (it could be well bound with the catalytic pocket of the pancreatic lipase). Pancreatic lipase is an important enzyme in the digestion of dietary triglycerides and its inhibition is a promising target in obesity treatment [24]. Thus, this cyclic-dipeptide could be a suitable candidate for obesity treatment.

Maculosin, cyclo-(L-Pro-L-Tyr): This neutral cyclic-dipeptide with 260 Da molecular weight is produced by some organisms, such as *Alternaria alternata*, the agent of black leaf blight of spotted knapweed [64] a novel moderately halophilic actinobacterium strain, related to *Streptomyces acrimycini* [65] *Bacillus subtilis* strain KN07 [66] *Streptomyces* sp. KTM18 [67] and *Streptomyces sp*. ZZ446. It shows diverse bioactivity, such as antimicrobial activity against methicillin - resistant *Staphylococcus aureus*, *E. coli*, and *Candida*

albicans [20] certain multidrug-resistant pathogenic bacteria [65] and antioxidant activity with no toxicity in brine shrimp lethality assay [67] This cyclic-dipeptide is probably a novel 2-C- methyl--erythritol 4-phosphate (MEP) pathway inhibitor [66] the pathway responsible for isoprenoids production [68] The presence of this pathway in pathogenic bacteria and some protozoa (including Plasmodium, the etiologic agent of malaria), not in humans, makes its enzymes suitable targets for the development of novel antibacterial drugs. The probable antimicrobial mechanism of this cyclic-dipeptide is inhibiting the enzymes of the MEP pathway. This pathway, which was discovered at the end of the 20th century, consists of seven enzymatic reactions: (I) condensation of glycelaldehyde-3-phosphate and pyruvate by DXP synthase (Dxs) and production of 1-deoxy-D-xylulose 5-phosphate (DXP); (II) then, DXP is converted to MEP by 1-deoxy-D-xylulose-5-phosphate reductoisomerase (Dxr); (III) MEP reacts with cytidine triphosphate for production of 4-diphosphocytidyl 2-C-methyl-D-erythritol (CDP- ME), is catalyzed by 4 diphosphocytidyl 2-C-methyl-D-erythritol cytidyltransferase (IspD); (IV) CDP-ME is phosphorylated by CDP-ME kinase (IspE); (V) then, converted to 2-C-methyl-D-erythritol 2,4-cyclodiphosphate (MEcDP), by MEcDP synthase (IspF); (VI) MEcDP is converted to 1-hydroxy-2-methyl-butentyl 4-diphosphate (HMBPP) by HMBPP synthase (IspG); (VII) finally, it is reduced to IPP or DMAPP by HMBPP reductase (LytB). According to the avidin-biotin complex and QCM experiments by Nakagawa et al [66] the IspG enzyme is a maculosin-binding protein and the hydro-xyl group of the L-Tyr residue in the maculosin moiety is essential for binding to IspG. Thus, maculosin is a novel inhibitor of the MEP pathway by binding to the IspG, the sixth enzyme on the MEP pathway [66] The schematic illustration of the MEP pathway and maculosin antimicrobial mechanism is shownin figure 1.

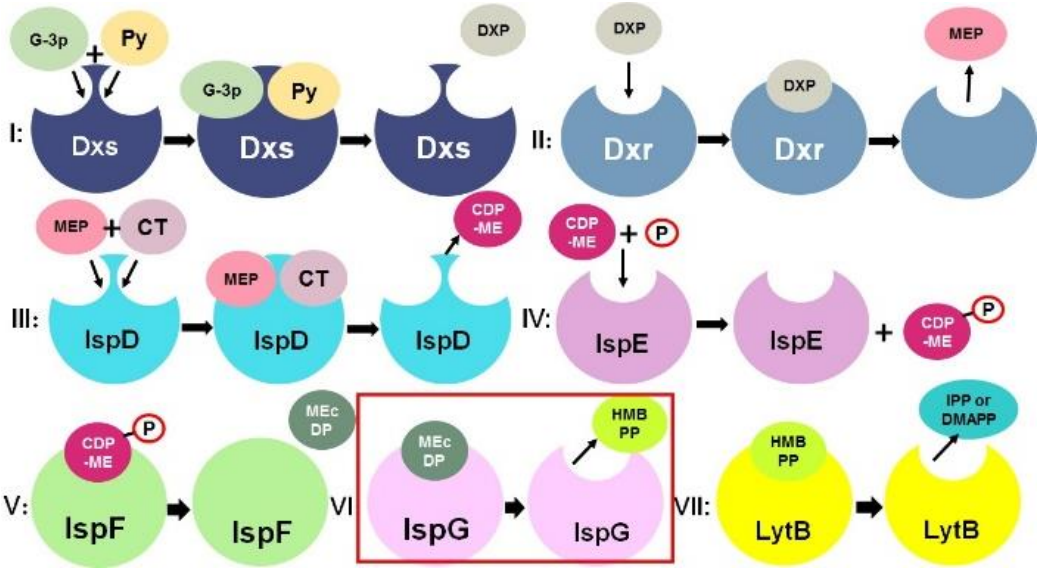


Figure 1. Schematic illustration of the MEP pathway and maculosin antimicrobial mechanism. G-3p: glycelaldehyde-3-phosphate; Py: pyruvate; Dxs: 1-deoxy-Dxylulose 5-phosphate synthase; Dxp: 1-deoxy-Dxylulose 5-phosphate; Dxr: 1-deoxy-D-xylulose-5-phosphate reductoisomerase; MEP: 2-C-methyl--erythritol 4-phosphate; CT: cytidine triphosphate; IspD: 4 diphosphocytidyl 2-C-methyl-D- erythritol cytidyltransferase; CDP-ME: 4-diphosphocytidyl 2-C-methyl-D-erythritol; P: phosphate; IspE: 4-diphosphocytidyl 2-C-methyl-D-erythritol kinase; MEcDP: 2-C-methyl-D-erythritol 2,4-cyclodiphosphate; IspF: 2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase; HMBPP: 1-hydroxy-2-methyl-butentyl 4-diphosphate; IspG: 1-hydroxy-2-methyl-butentyl 4-diphosphate synthase; LytB: 1-hydroxy-2-methyl- butentyl 4-diphosphate reductase; IPP: isopentenyl pyrophosphate; DMAPP: dimethylallyl pyrophosphate. Maculosin could inhibite this pathway by bonding to the IspG enzyme (VI stage), that is shown by a red box in the picture.

6.2. Recent advancements in design and engineering of cyclic peptides

Secondary metabolites derived from *Streptomyces* have significantly expanded their therapeutic potential and paved the way for the development of novel drug candidates. In this section, we highlight key strategies and innovations in this field [69]

Genomic mining and bioinformatic analysis: The advent of genomic mining and bioinformatic analysis has revolutionized the discovery and characterization of cyclic peptides encoded within the genomes of *Streptomyces* bacteria [70]. Researchers leverage next-generation sequencing technologies and computational algorithms [71] to systematically identify biosynthetic gene clusters responsible for cyclic peptide biosynthesis. Furthermore, bioinformatics tools enable the prediction of peptide sequence, structure, and bioactivity, facilitating the rational design and engineering of cyclic peptides with desired properties [72,73]

Synthetic biology and metabolic engineering: Synthetic biology and metabolic engineering approaches offer powerful tools for the heterologous expression and biosynthesis of cyclic peptides in engineered *Streptomyces* strains. By manipulating biosynthetic pathways and enzyme activities, researchers can enhance the production titers, structural diversity, and pharmacological potency of cyclic peptides. Moreover, synthetic biology techniques enable the creation of designer cyclic peptide libraries through combinatorial biosynthesis and directed evolution strategies, enabling the generation of novel analogs with improved pharmacokinetic profiles and target specificity [74,75]

Structure-activity relationship studies: Structure-activity relationship (SAR) studies play a crucial role in elucidating the molecular determinants of cyclic peptide bioactivity and optimizing their pharmacological properties. Recent advancements in SAR studies have shed light on the structural features of cyclic peptides that govern target binding, cell permeability, and metabolic stability. By systematically modifying amino acid residues, cyclization motifs, and side-chain functionalities, researchers can fine-tune the potency, selectivity, and ADME (absorption, distribution, metabolism, and excretion) properties of cyclic peptides derived from *Streptomyces* secondary metabolites [76]

7. Peptide engineering and chemical modification

Peptide engineering and chemical modification strategies offer versatile approaches for enhancing the pharmacological properties and biophysical characteristics of cyclic peptides. Recent advancements in peptide engineering techniques, such as peptide stapling, backbone cyclization, and side-chain modification, have enabled the generation of cyclic peptides with improved proteolytic stability, membrane permeability, and target affinity. Furthermore, chemical modifications, such as glycosylation, lipidation, and PEGylation, can modulate the pharmacokinetic profile, biodistribution, and immunogenicity of cyclic peptides, thereby enhancing their therapeutic efficacy and safety [73]

8. Nanotechnology and drug delivery systems

Nanotechnology-based drug delivery systems hold promise for overcoming the challenges associated with the delivery of cyclic peptides derived from *Streptomyces* secondary metabolites. By encapsulating cyclic peptides within nanoparticles, liposomes, or polymeric carriers, researchers can enhance their solubility, stability, and bioavailability. Moreover, targeted delivery strategies, such as ligand-mediated targeting and stimuli-responsive release, enable selective accumulation and controlled

release of cyclic peptides at the site of action, minimizing off-target effects and improving therapeutic outcomes [77]

9. Discussion

Antimicrobial peptides (AMPs), which have been interesting today, due to increasing bacterial antibiotic resistance, are protein-like molecules that often contain altered and modified amino acids that are not found in polypeptides made by ribosomes. These peptides include two groups of bacteriocins and peptide antibiotics. There are some limitations in using AMPs for therapeutic purposes such as hemolytic activity on the eukaryotic cells, low bioavailability, and high manufacturing cost. Thus, producing recombinant AMPs to remove the mentioned restrictions is valuable [1] AMPs are produced by many microorganisms one of which is *Bacillus* spp., and much research has been done on this genus [4-5] *Streptomyces* are the other bacteria-producing AMPs. This spore-forming gram-positive bacteria belonging to the phylum Actinobacteria, have aerial hyphae for reproduction [6] *Streptomyces* produce some groups of antibiotics as secondary metabolites such as lipopeptides, 2,5-diketopiperazines (DKPs) or cyclic dipeptides, dimeric peptides, nucleosidyl peptides, thioamide-containing peptides, thiopeptides, lasso peptides or lariat peptides, and typical cyclic peptides [7] In this paper, we focused on dipeptides produced by *Streptomyces* sp.

Cyclic-dipeptides are cyclodipeptides resulting from the "tail to head" cyclization of two amino acids. This neutral compounds with antibacterial, antiviral, anticancer, and antifungal activities, are more stable compared to linear dipeptides due to the lack of free amine or acid terminal. Cyclic-dipeptides could be extracted by ethyl acetate (EtOAc) as the solvent [13] and purified by HPLC [19].

Among many cyclic-dipeptides produced by *Streptomyces*, some of them with multifunctional activities are more important. For example, Cyclo-(L-Pro-L-Val) with anticancer [30] antibacterial [31] and Quorum quenching activities [56] Cyclo-(L-Pro-D-Leu) with anticancer [30] and antifungal effect by inhibiting aflatoxin production [32] Cyclo-(L-Pro-L-Leu) with broad spectrum inhibition effects against cancer cell lines [30] gram-positive and gram-negative bacteria, and fungi [32] and Brevianamide F with anticancer [63] antibacterial [40] and antifungal [42] activities, are some of broad spectrum cyclic-dipeptides in *Streptomyces*.

One of the important aspects of AMP application in human therapeutic purposes is non-toxicity on the eukaryotic cells. 2-C- methyl--erythritol 4-phosphate (MEP) pathway, the pathway responsible for isoprenoids production [68] is unique to bacteria and some protozoa, not in humans. So MEP pathway inhibition could be a safe method for limiting pathogens, without human toxicity. Maculosin is probably a novel MEP pathway inhibitor [66]. According to the avidin-biotin complex and QCM experiments by Nakagawa et al [66] the IspG enzyme is a maculosin-binding protein and the hydroxyl group of the L-Tyr residue in the maculosin moiety is essential for binding to IspG. Thus, maculosin is a novel inhibitor of the MEP pathway by binding to the IspG, the sixth enzyme on the MEP pathway [66].

According to the importance of cyclic peptides as a novel therapeutic purpose and the need to reduce toxicity and increase their antimicrobial and anticancer effects, designing and engineering cyclic peptides is crucial for reaching these goals. Genomic mining and bioinformatic analysis [70-73], synthetic biology and metabolic engineering [74-75], structure-activity relationship studies [76], peptide engineering and chemical modification [73-78] and nanotechnology and drug delivery systems [77] are recent advancements in the design and engineering of cyclic peptides.

10. Conclusion

As increasing microbial resistance to the usual antibiotics, investigation of novel antimicrobial substances is crucial. Antimicrobial peptides (AMPs) are one of the important antimicrobial agents, which are produced by many organisms such as bacteria. *Streptomyces* is the bacterial strain producing many groups of AMPs, one of which is cyclic dipeptides. This paper reviews dipeptides and cyclic dipeptides produced by *Streptomyces*. Some of these metabolites have multifunctional activities, which are more valuable for therapeutic purposes. Also, the design and engineering of these metabolites could lead us to the goal of reducing their toxicity and increasing their effectiveness. Based on the provided search results, *Streptomyces*-derived dipeptides and cyclic dipeptides can be classified primarily by their structure and biosynthetic origin. The most classification is based on molecular structure. Linear Dipeptides, consist of two amino acids linked by a single peptide bond in an open chain like Ala-azaserine and alahopcin .Cyclic Dipeptides (2,5-Diketopiperazines, DKPs) These are the smallest cyclic peptides, such as cyclo(Pro-Leu), cyclo(Pro-Val), and cyclo(Phe-Phe), have been isolated from *Streptomyces* species .Cyclic dipeptides are also classified by their biosynthetic pathway, Cyclodipeptide Synthase Dependent, This pathway is common in bacteria, including *Streptomyces* CDPS (Cyclodipeptide Synthase Dependent enzymes) are relatively small (200–300 amino acids) and use activated aminoacyl-tRNAs as substrates to build the cyclic dipeptide ring. NRPS (No ribosomal Peptide Syntheses) while more common in fungi and bacillus, NRPS pathways also contribute to the production of cyclic dipeptides in *Streptomyces*. These enzymes are large, multi-modular complexes that activated free amino acids.

11. Declarations

11.1. Acknowledgements

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11. 2. Conflict of Interest

The authors declare no conflict of interest.

11.3. Authors Contributions

Formal analysis and graphic investigation, Ftemeh Sadat Ghoreishi, writing-original draft preparation, Fatemeh Yousef-Saber. writing-review and editing, Giti Emtiazi, supervision,Giti Emtiazi, project administration, personal.

11.4. Using Artificial Intelligent chatbots

AI chatbots used for graphic abstract and Protein data bank were used in this research.

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