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PROSPECTS OF CYCLIC DIPEPTIDES AS POTENTIAL BIOMATERIALS WITH DIVERSE BIOLOGICAL FUNCTIONALITIES: A REVIEW

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ABSTRACT

Cyclic dipeptides (CDPs) represent a diverse group of biologically active organic molecules having broad-spectrum pharmacological and bioactive potentialities. Over the recent decade, CDPs have garnered considerable interest due to their broad applications, particularly in biomedical sciences such as targeted drug delivery, wound healing, and tissue engineering. In addition, CDPs have been studied for bacterial quorum sensing applications, which enable communication about population size and the regulation of a behavioral switch from symbiosis with their host to virulence. CDPs can be prepared using various bio-based and chemical methods. Naturally, CDPs are produced by different microorganisms, sponges, plants, and animal species. Several versatile synthetic CDPs have been designed with the desired configuration, ring size, yield, and properties to target highly specific biological pathways. The structural ability of CDPs enables them to bind with multiple unrelated classes of biological targets, resulting in remarkable biological activities, including neuroprotective, anticancer, antioxidant, and antimicrobial (antiviral, antibacterial, and antifungal) potential. Owing to their robust stability and excellent rheological properties, these materials are highlighted as promising candidates in pharmacological biomaterials and current therapeutics in this article.

Keywords: Bioactive peptides; Cyclic dipeptides; Synthesis routes; Bioactive potential; Pharmacological applications.

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1. INTRODUCTION

Cyclic dipeptides or CDPs [other names 2,5-diketopiperazines (DKPs); cyclo(dipeptides) and dipeptide anhydrides] are the simplest cyclic forms of peptides commonly found in nature (Fizza et al. 2025). CDPs are considered as the fermentation products of various microbial species (Saadouli et al. 2020; Apostolopoulos et al. 2021). CDPs were denied as a special class of biologically active compounds till the early twentieth century. Initially, the simplest dipeptide [cyclo(Gly-Gly)] was synthesized in the ninetieth century to determine their bioactive potentials (Gesellchen and Santerre 2024). CDPs hold two cis-amide bonds which render them to make four H-bonding sites (pair of acceptor and donor sites) for the binding with receptors and different enzymes. Due to flexibility and semi-rigidity, a variety of shapes (planner, chair, or boat conformation) has been suggested for CDPs found in solid, liquid, and gaseous states (Lee 2022). CDPs have been shown to be biologically active molecules owing to their cyclic and stable conformations. They differ from other cyclic peptides in some properties such as, (i) they act as neutral compounds rather than zwitterions, (ii) they exhibit solubility in aqueous media, and (iii) they have potential to damage the globular protein structure (Touve et al. 2019; Mitra and Sarkar 2020). CDPs have also some remarkable structural properties such as rigid conformation, resistance to proteolysis, stable under a wide range of pH, mimic some peptide pharmacophoric groups, H-bond acceptor, and H-bond donor groups to interact with target biomolecules. These attractive properties make them desired candidates to formulate new therapeutic interventions through combinatorial chemistry approaches (Pandurangan et al. 2020). Several reports are available showing excellent antimicrobial (Abdel Monaim et al. 2019), anti-mutagenic (Nedal et al. 2020), antiviral [influenza virus A, SARS-CoV-2 (COVID-19)] (Manna et al. 2020), anticancer (Sabernavaei et al. 2024), neuroprotective (Thapa et al. 2021), and cardio-protective (Siaravas et al.

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2025) properties. Different CDPs, including cyclo(Ile-Val), cyclo(Pro-Leu), cyclo(Pro-Val), cyclo(Leu–Pro), and cyclo(Phe–Pro) have been widely reported among therapeutically-active peptides (Fidor et al. 2020; Kong and Heinis 2021). Following the biological activities and broad-spectrum applications of cyclic dipeptides in the biomedical sector, this review aims to summarize the current knowledge available on the production methods of cyclic dipeptides, including both bio-based and chemical syntheses. The diverse biological potentialities of cyclic dipeptides, including neuroprotective, anticancer, antimicrobial (antibacterial, antifungal, and antiviral), and antioxidant properties, make them promising candidates for various biomedical applications, such as quorum sensing and hydrogel formation for biomedical and pharmacological purposes.

2. SYNTHESIS ROUTES OF CDPS

2.1. Biological Synthesis

Linear dipeptides and CDPs are abundant biomolecules, which are produced naturally by different microbial species including *Lactobacillus coryniformis* (Salman et al. 2022), *Lactobacillus plantarum* LBP-K10 (Kwak et al. 2018), *Candida albicans* (Kim et al. 2019), *Neobacillus drentensis* (Routhu et al. 2021), *Aspergillus* and *Penicillium* (Bushman et al. 2023), *Alternaria alternata* (Qader et al. 2021) and *Orchidaceae* family (Jakubska-Busse et al. 2021). These compounds are generally synthesized during fermentation of microorganisms and the proteolysis of large proteins and peptides in mammals.

2.1.1. Non-ribosomal peptide Synthetases (NRPS): Non-ribosomal peptide Synthetases (NRPS) have been considered responsible for non-ribosomal synthesis of CDPs. NRPSs are multifunctional and modular mega-enzymes that have long been considered for the non-ribosomal synthesis of CDPs and macrocyclic compounds (Wang et al. 2019). Each module is designed for a specific amino acid monomer and is required for the elongation of the peptide chain. The module contains three major domains: (i) the A-domain, which is responsible for amino acid recruitment and activation as acyl-adenylate A-domain; (ii) the second domain is the peptidyl-carrier-protein (PCP) domain to which all intermediates are bound covalently. PCP domain is also known as 4-phosphopantetheine cofactor binding site; (iii) the third is the condensation domain (C), which is responsible for the peptide bond formation between two adjacent PCP-intermediate module complexes (Süssmuth and Mainz 2017; Corpuz et al. 2022). In addition to these three domains, another domain, [named thioesterase (TE)] is also present, which is responsible for the release of peptide product. The order of domain assembly is C-A-PCP-TE. In some cases, NRPS associated with the formation CDPs lack TE domain. This TE domain is replaced by the C domain, which is considered for cyclization of linear dipeptides with subsequent release of CDPs (Mishra et al. 2017). Cyclization (Cy) domain is responsible for the cyclization of these peptides (Fig. 1). Cyclo(D-Phe-L-Pro) (Ashigai et al. 2018) and cyclomarazine (Schultz et al. 2008) are CDPs which are produced as side products during tyrocidine and cyclomarin biosynthesis by NRPS, respectively. Tyrocidine is a decapeptide product of TycA, TycB, and TycC NRPS. During the tyrocidine formation, phenylalanine and proline are combined by TycA and remain covalently bound to the enzyme. Proline makes *cis*-conformational constraints resulting in the cyclization and subsequently early cyclo(D-Phe-L-Pro) release (Ashigai et al. 2018). Dedicated NRPSs produce different types of CDPs such as thaxtomin A (Liu et al. 2021), fumitremorgin C, roquefortine C (Stierle 2023), acetylaszonalenin (Sun et al. 2022), gliotoxin (Widodo and Billerbeck 2023) and sirodesmin (Urquhart et al. 2021) in different microbial species.

2.1.2. Cyclodipeptide Synthases (CDPS): Cyclodipeptide synthases (CDPS) are another class of small enzymes which can catalyze the CDPs production during albonoursin biosynthesis pathway (Le Chevalier et al. 2020). These enzymes utilize aminoacyl-tRNAs (aa-tRNAs) as substrate, and catalyze two peptide bonds without using ATP, resulting in the formation of a cyclic dipeptide by the sequential ping-pong method (Widodo and Billerbeck 2023). CDPS capture aa-tRNAs and use them for the production of cyclic dipeptides by diverting them from protein synthesis machinery, ultimately presenting a connection between primary and secondary metabolism. Until now, more than 50 CDPS gene clusters have been identified in different phyla of bacteria, algae, fungi, and animals using Position-Specific Iterative-Basic Local Alignment Search Tool (PSI-BLAST) (Available at: https://www.ebi.ac.uk/Tools/sss/psiblast/). Newly synthesized CDPs can be modified by tailoring enzymes present near to the respective CDPS's genetic loci (Skinnider et al. 2018; Canu et al. 2020). The CDPS pathway captures amino acids by aminoacyl tRNA during protein synthesis, resulting in the formation of aminoacyl-CDPS intermediate. In the next step, CDPS binds with another aminoacyl tRNA forming dipeptide-CDPS complex. The CDPS breaks the bond between the dipeptide and tRNA, making the dipeptide readily available in the biological system (He et al. 2024; Fizza et al. 2025). The general mechanism of CDP synthesis by the CDPS pathway is described in Table 1 and illustrated in Fig. 2 (Shinoda and Miura 2024).

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Table 1: Natural synthesis of cyclic dipeptides by various microbial species, their source of isolation, and potential biological activities.

Cyclic dipeptides	Producing microorganism	Source of isolation	Biological activities	References
cyclo(L-Pro-D-Met), cyclo(D-Pro-D-Leu), cyclo(L-Pro-D-Phe), cyclo(L-Pro-L-Val)	*Bacillus cereus*	Sweet potato weevil grubs/ Nematode infested *G. mellonella* larvae	Antibacterial activity, antifungal activity	(Hirt et al. 2020)
cyclo(L-Leu-L-Pro)	*Bacillus amyloliquefaciens* (MMS-50)	Mangrove rhizosphere soil	Antibiofilm, antiviral activity against MRSA	(Chen et al. 2025)
cyclo(Pro-Val)	*Pseudomonas frederiksbergensis* CMAA 1323	Antarctic hair grass *Deschampsia antarctica*	Antifungal activity against *Botrytis cinerea*	(Khalifa et al. 2022)
cyclo(L-Leu-L-Pro)	*Bacillus amyloliquefaciens*	Marine bacteria	Antiviral activity against *Listeria monocytogenes*	(Bushman et al. 2023)
14-hydroxy-cyclopeptine	*Aspergillus sp.* SCSIOW2	Marine sediment (South China Sea)	Nitric oxide inhibition	(Hafez Ghoran et al. 2023)
Penicimutide, cyclo(L-Val-L-Pro), cyclo(L-Ile-L-Pro), cyclo(L-Leu-L-Pro), cyclo(L-Phe-L-Pro)	*Penicillium purpurogenum* G59	Soil	Anticancer activity	(Hafez Ghoran et al. 2023)
cyclo(L-Leu-L-Pro)	*Bacillus amyloliquefaciens* MMS-50	Mangrove rhizosphere	Antibiofilm efficacy against *Staphylococcus epidermidis* RP62A	(Romero-Diaz et al. 2020)
cyclo(L-Leu-L-Pro)	*Veillonella tobetsuensis*	Oral cavity	Biofilm inhibition of *Streptococcus gordonii*	(Li et al. 2022)
cyclo(L-Pro-D-Ile), cyclo(L-Pro-L-Phe)	*Escherichia coli*	Soil	Antimicrobial activity against *Ralstonia Solanacearum*	(Zhao et al. 2021)
cyclo(Pro-4-hydroxy-Leu), cyclo(L-Ala-L-Val), cyclo(L-Pro-L-Tyr)	*Coprinus plicatilis*	-	Cytotoxicity against SK-BR-3, A-549, HL-60, SMMC-7721, PANC-1 cell lines	(Zhao et al. 2019)
cyclo(R-Pro-S-Phe), cyclo(R-Pro-R-Phe)	Marine derived *Penicillium sp.*	Red Sea tunicate *Didemnum* sp.	Antiproliferative, cytotoxic, and antimicrobial activity	(Youssef and Alahdal 2018)
cyclo(L-Pro-L-Val), cyclo(L-Leu-L-Pro)	*Pseudomonas cedrina*	*Pinus patula* stem tumors	Antiproliferative activity against human HeLa, lung (A-549), breast (HBL-100) cell lines	(Sánchez-Tafolla et al. 2019)
cyclo(L-Leu-L-Pro)	*Bacillus amyloliquefaciens*	Mangrove rhizosphere	Anti-quorum sensing efficacy against *S. marcescens*	(Gowrishankar et al. 2019)
cyclo(Leu-Pro), cyclo(Val-Pro), cyclo(Leu-hydroxy-Pro), cyclo(Pro-Tyr), cyclo(Pro-Ala), cyclo(Gly-Pro)	*Pseudomonas sp.* ABS-36	Rhizospheric soil	Anti-inflammatory activity by cytokine inhibition	(Ahil et al. 2019)
Cyclic peptide ASP-1	*Bacillus subtilis*	-	Antimicrobial activity against MRSA	(Deshmukh et al. 2021)
Cyclic lipopeptide C15-bacillomycin D	*Bacillus velezensis* NST6	Soil samples	Anti-staphylococcal activity	(Nam et al. 2021)
cyclo(L-Leu-L-Pro)	*Pseudomonas fluorescens*	Marine sponges	Anticancer activity	(Kim et al. 2023)
cyclo(Leu-Pro)	*Actinomycete strain* KH-614	Soil sample	Anticancer activity	(Bojarska et al. 2021)
Petrocidin A	*Streptomyces* sp. SBT348	soil sample	Anticancer activity	(Rammali et al. 2024)
cyclo(L-Pro-D-Arg)	*Bacillus cereus*	Hemolymph of nematode-infested *Galleria mellonella* larvae.	Anticancer activity	(Son et al. 2024).
Cis-cyclo(L-Leu-L-Pro) and cis-cyclo(L-Phe-L-Pro)	*Lactobacillus plantarum* LBP-K10	fermented plants	Antiviral activity against influenza A virus (H3N2)	(Son et al. 2024).
Cyclo(Leu-Pro)	*Bacillus amyloliquefaciens*	Marine origin	Prevented virulence and biofilm production in MRSA	(Díaz et al. 2022)
cyclo(D-Pro-L-Val)	*Bacillus amyloliquefaciens* Y1	Field soil	Antifungal activity against *Fusarium graminearum*	(Maung et al. 2021).

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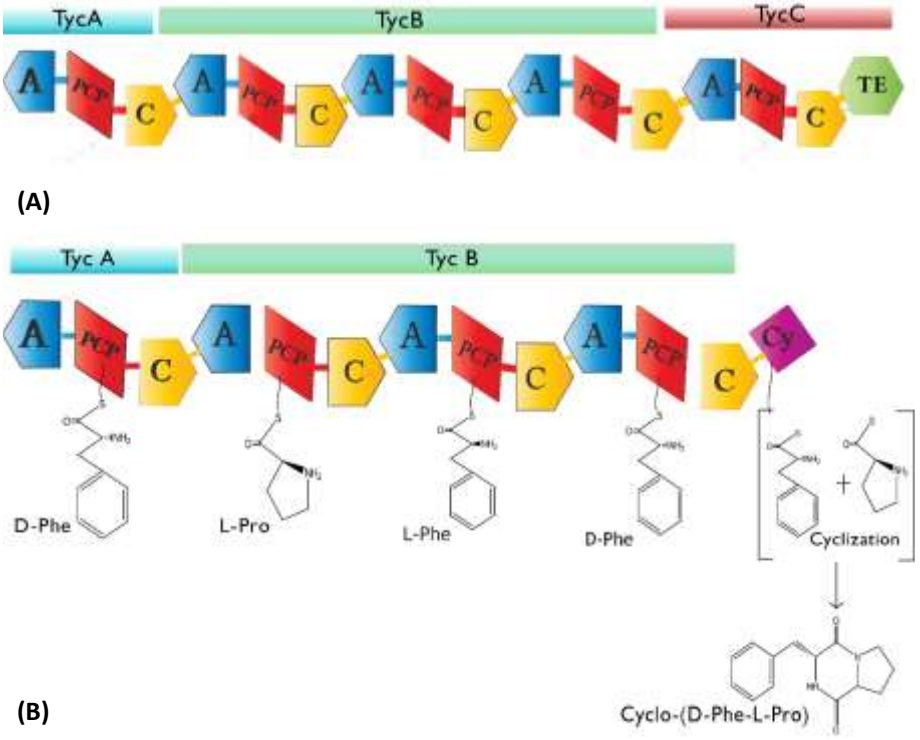

Fig. 1: CDP synthesis by NRPS: (A) Tyrocidine synthesis by NRPS TycA, TycB, TycC. (B) CDP forming NRPS lacks TE domain, which is replaced by Cy domain, crystallization at Cy domain results in release of cyclo(D-Phe-L-Pro) as side product. (Abbreviations A: domain A; C: domain C; PCP: peptidyl-carrier-protein domain; TE: thioestrase domain; TycA, TycB, TycC: NRPSs involve in tyrocidine synthesis; Phe: phenylalanine; Pro: proline; Cy: Cyclization domain)

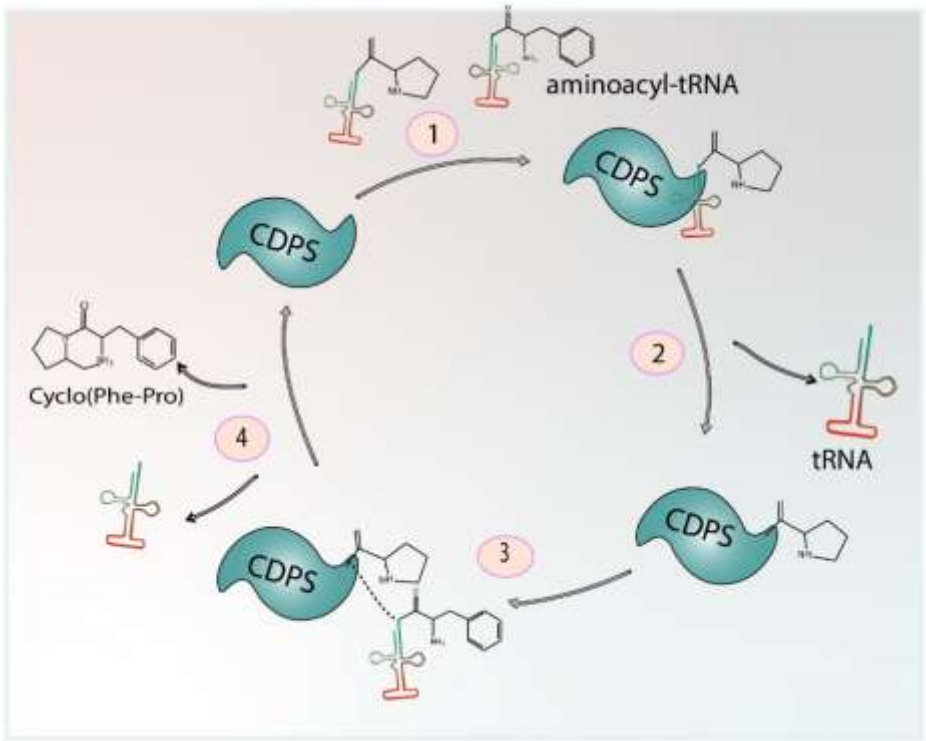

Fig. 2: CDP synthesis by cyclodipeptide synthase (CDPS): (1) CDPSs hijack amino acids carried by aminoacyl t-RNAs of protein synthesis pathway. (2) Formation of aminoacyl-CDPS intermediate. (3) dipeptide-CDPS intermediate is formed when another aminoacyl t-RNA molecule attaches with aminoacyl-CDPS complex. (4) The dipeptide and t-RNA detaches from the CDPS again making it readily available. Adapted from with permission.

Three modified CDPs albonoursin (*Streptomyces noursei*) (Ren et al. 2025), mycocyclosin (*Mycobacterium tuberculosis*) (Fizza et al. 2025), and pulcherriminic acid (*Bacillus subtilis*) (Pan et al. 2024) are the products of CDPS-dependent pathways. In case of albonoursin synthesis, *Streptomyces noursei* contains four genes, albA-D, which together are responsible for the albonoursin production and export. AlbC catalyzes the peptide bond to produce cyclo(L-Phe-L-Leu) (cFL) precursor, while albA and B carry out α, β-dehydrogenation by tailoring enzyme cyclodipeptide oxidase converting cFL to albonoursin (modified CDP) and albD encodes membrane proteins (Mikulski et al. 2020). Pulcherrimin biosynthesis involves pulcherriminic acid formation by aromatization of

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cyclo(Leu-Leu) accompanied by double N-oxide formation by *Bacillus subtilis* cytochrome P450 (Yuan et al. 2020). Mycocyclosin is produced by oxidative C-C bond formation from cyclo(L-Tyr-L-Tyr) catalyzed by cytochrome P450 enzyme (Freytag et al. 2024). Nocazines represent another class of tailored hydrophobic CDPs produced by CDPS-dependent pathway. In a study, three new CDPs were reported to be produced by CDPS-dependent pathway in *Nocardiopsis dassonvillei* HR10-5 (Chen et al. 2019).

2.2. Chemical Synthesis

Different procedures for the chemical synthesis of CDPs have been reported in literature. CDPs could be synthesized chemically from their linear counterparts in solution phase as well as on solid phase (Ghosh et al. 2024). Ugi reaction, microwave heating, and phase transfer catalysis (PTC) methods are of great interest (Divyavani et al. 2025). Mechanisms of different chemical syntheses routes of CDPs have been represented in Fig. 3.

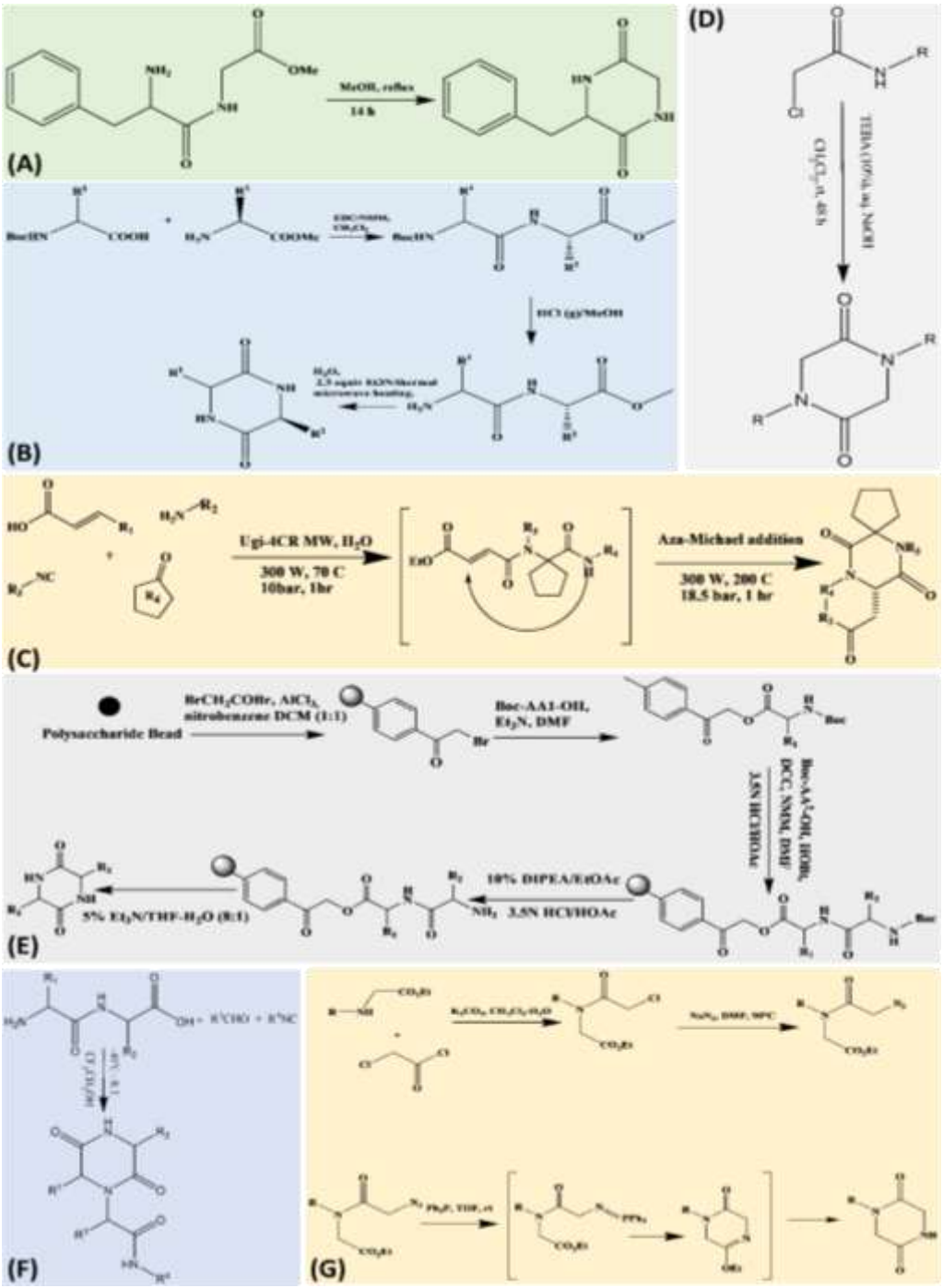

Fig. 3: Chemical syntheses routes of CDPs along with reagents and processing conditions: (A) Solution phase synthesis (Bhukta et al. 2023; Fizza et al. 2025); (B) Microwave-assisted synthesis (Ghosh et al. 2024); (C) Aza-Michael Addition; (D) Phase transfer catalysis (Scarel and Marchesan 2021); (E) Solid phase synthesis; (F) Synthesis of CPDs by Ugi reaction (Bechtler and Lamers 2021); (G) Aza-Wittig reaction (Mitasev et al. 2021).

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2.2.1. Solution Phase Synthesis: Generally, solution phase synthesis of cyclic dipeptides is carried out by mixing triethylamine and diethyl-phosphoryl cyanide to stirred solution of N-t-Boc-L-X(a.a) and L-X(a.a)-OMe in 1,2 dimethoxyethane at 0°C. After 1h at 0°C or 4h at room temperature, the reaction mixture is diluted with chloroform and washed with HCl, aqueous $NaHCO_3$, and saturated brine, which results in the formation of protected N-t-Boc dipeptide esters. N-t-Boc dipeptide esters are dissolved in formic acid, which results in the formation of crude dipeptide esters (Balachandra et al. 2021). These crude dipeptides are cyclized in the presence of butanol and toluene for 3h at 120°C (Veer et al. 2021). The solution product is recrystallized by appropriate solvent, yielding the cyclic dipeptides after concentrating and cooling (Fig. 3A). In general, solution phase synthesis includes dipeptide methyl ester cyclization or direct cyclization of unprotected dipeptide (Scarel and Marchesan 2021). These methods comprise some limitations, e.g., in the Fischer method, methyl esters are cyclized in excess of ammonia, resulting in epimerization and peptide cleavage (Naumann 2023), ultimately decreasing production even at high temperature and long reaction time.

2.2.2. Microwave-Assisted Synthesis: This method involves three steps, (i) N-Boc-protected amino acid is coupled with an amino acid methyl ester to form dipeptides using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC); (ii) Boc-group is removed using HCl-saturated methanol to make dipeptide methyl ester hydrochloride salts, and (iii) dipeptides are cyclized in the presence of triethylamine as base (Fig. 3B) (Devi et al. 2021). In the last decade, several studies have reported thermal and microwave heating as highly effective methods. In microwave heating, dipeptides methyl ester hydrochlorides are cyclized by microwave-assisted heating, yielding moderate to high (63-97%) product recovery (Kumar et al. 2018; Mukhia et al. 2023). Microwave flash-heating reduces the reaction time from the conventionally used methods and enhances the intramolecular coupling yield of CDPs. Effective one-pot reaction of Ugi-4C conjugate reaction/intramolecular Aza-Michael addition of resonance-stabilized carbanions form 2,5-DKP ring under the influence of microwaves without utilization of additional reagents. Microwaves are used as a source of heating as conventional methods do not give 2,5-DKP ring as a product in direct conversion of 4-CR. It is a two-step conjugate reaction between aldehydes, isocyanides, amines, and protic solvent gives acyclic Ugi adduct. This intermediate Ugi adduct under the influence of microwave (300W, 200°C, and 18.5bar) in the presence of solvent leads to intramolecular amide N-alkylation, resulting in the formation of spiro-2,5-DKP. Using different bifunctional substrates, a variety of 2,5–DKP structures can be obtained in good to excellent yield (50-85%) using this one-step protocol (Fig. 3C) (Gao et al. 2021).

2.2.3. Phase Transfer Catalysis (PTC): PTC synthesis is an effective method to obtain high yield (up to 90%), which employs single-step direct cyclization of N-substituted chloro-acetamides/amino acids at room temperature. This method is performed in the presence of a phase transfer catalyst, triethylbenzylammonium chloride (TEBA), in the two-phase medium (CH_2Cl_2/alkaline solution) (Wang 2019). Generally, low reactant concentrations and high dilutions result in cyclization and high reactant concentration favoring polymerization. In contrast, high selectivity towards cyclization even at higher reactant concentration. The optimal ratio of TEBA/chloroacetamide was reported to be 10% (w/w) of catalyst/amide, which reacts with chloroacetamide yielding high product recovery (Fig. 3D) (Velambath et al. 2023).

2.2.4. Solid-Phase Synthesis: Solid-phase synthesis is a multistep process, widely used to produce the DKPs with variations in type of protecting groups, resins, and cleavage type (Li et al. 2024). In this method, first step involves the fixation of C-terminal of amino acid using phenacyl ester (*O*-Pac) bond, and N-terminal fixation using carbamate bond with a variety of resins such as polystyrene resin, Merrifield resin, bromoacetyl resin, phoxime resin, Wang resin, and others (Ramkisson 2018). The second step involves deprotection of Boc-amino acid and coupling of the next amino acid forming the dipeptide. Finally, the cyclization of the synthesized dipeptide by intramolecular aminolysis and release of the cyclic dipeptide successively from the resin is carried out (Fig. 3E) (Bechtler and Lamers 2021). Solid-phase synthesis is more advantageous than the conventionally used step-by-step solution phase method. Among technologies developed for large-scale production of peptides, solid-phase synthesis is a promising technology for peptide synthesis. In solid-phase synthesis, a chemist can synthesize peptides of varying lengths of di- and/or tripeptides or even up to 20-50 amino acid length. Solid-phase synthesis is used in combination with solution-phase synthesis (hybrid system) when synthesizing peptides up to 60 amino acids in length (Naoum et al., 2022).

2.2.5. Synthesis by Ugi Chemistry: For the synthesis of DKPs, Ugi's reaction is a mechanism containing multistep process, which allows substitution at the second amino group to form acyclic dipeptide precursor. Ugi's reaction employs the use of amine, aldehyde, amino acid, and isonitrile (Pecchini et al. 2024) and produces a high yield of dipeptides with optical purity (Larghi et al. 2024). The major advantage of Ugi reaction is the product variety due to Ugi reactants-aldehyde, amine, and carboxylic acid, which are required for peptide coupling to the amino acid and

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are used to produce DKPs library. The major drawback of Ugi reaction is the difficulty in cyclic dipeptide formation due to the production of C-terminal amide which hinders cyclization of dipeptide (Fig. 3F) (Bechtler and Lamers 2021).

2.2.6. Aza-Wittig Reaction: Aza-Witting reaction is an azide reduction reaction that is also known as Staudinger reaction. Different *N*-substituted DKPs can be obtained with high yield (88-96%) under mild reaction conditions from amino ester molecules using the intramolecular Aza-Wittig reaction. Azide compound prepared from amide is obtained from amino ester acylation of chloroacetyl chloride followed by the treatment with sodium azide. Azide reacts with triphenylphosphine (reducing agent) in THF, nucleophilic addition of phosphine at terminal nitrogen of azide and expulsion of nitrogen gives imino-phosphorane. The intermediate is hydrolyzed to produce amine and triphenylphosphine oxide. The imino-phosphorane readily cyclizes to form an imino ether, which, in moist THF, yields the 2,5-diketopiperazine (DKP) product (Fig. 3G) (Mitasev et al. 2021).

3. BIOLOGICAL ACTIVITIES OF CYCLIC DIPEPTIDES

CDPs are considered privileged structures due to their structural stability and high-affinity binding with various classes of biological targets. Remarkable biological activities have been reported by different members of CDP family including antifungal (Kim et al. 2019; Gajbhiye and Kapadnis 2021), antiviral (Lee et al. 2018; Manna et al. 2020), antitumor (Bai et al. 2021; Wei et al. 2021), antibacterial (Schnaider et al. 2017; Tsai et al. 2020), antihypertensive (Lin et al. 2018; Jahandideh and Wu 2020), neuroprotective (Li et al. 2021), cytoprotective (Tan et al. 2019; Deepak et al. 2021), antioxidant (Manchineella et al. 2017; Schmeda-Hirschmann et al. 2020), chitinase inhibition (Kumar and Zhang 2019; Bojarska and Wolf 2020), quorum sensing (Zhu et al. 2019; Sun et al. 2020; Yu et al. 2021), antiarrhythmic (Bojarska and Wolf 2020), antihyperglycemic (Zhu et al. 2019; Ye et al. 2021) and analgesic (Santos et al. 2018; Ueda 2021), which make them interesting candidate to explore their applications in pharmaceutical drug formulations.

3.1. Neuroprotective Activity of CDPs

There has been an increasing concern about the development of multifunctional neuroprotective agents which can target multiple mechanisms in traumatic brain or spinal cord injury. Clinical neuroprotective strategies have been directed at the modification of individual components to delay the complex secondary injury biochemical cascade that occurs after the neurotrauma. One of the multipotential treatment approaches could be the use of small biologically active diketopiperazines and their derivatives (Li et al. 2021). The concept of CDPs scaffold as novel family of brain drug delivery system using CDPs as blood-brain-barrier shuttles (BBB-shuttles) for drug delivery of poorly BBB-permeable compounds. Naturally occurring tripeptide hormone L-pyroglutamyl-L-histidyl-L-prolinamide or thyrotropin-releasing hormone (TRH) plays excellent neuromodulatory effects in central nervous system (CNS) (Gudi et al. 2023). Hypothalamic neuropeptide TRH exhibits improvement in neurological recovery after neurotrauma; however, the clinical use of TRH is limited due to its autonomic and endocrine action and rapid enzymatic degradation (Dwyer et al. 2023). Enzymatic cleavage of TRH by thyroliberinase gives biologically active cyclo(His-Pro) peptide which exhibits wide range of neuroprotective and cytoprotective effects against cellular oxidative stress (Kobayashi and Kihara 2021). Minelli and his coworkers investigated the cytoprotective effects of cyclo(His-Pro) on cellular proliferation under experimental conditions, which causes cellular stress in PC12 cell culture model protecting the cells from apoptosis. Neuroprotection is correlated to a mechanism involving Nrf2 activation that increases glutathione production and decreases reactive oxygen species (ROS) synthesis (Hannan et al. 2020). Cyclo(His-Pro) interferes with Nrf2– ERK1/2 systems coupled with G_s and G_q proteins. It also shows protective response against paraquat neurotoxicity by up-regulating Keap1/Nrf2 pathway, which leads to the transcriptional activation of heme oxygenase and GCL (γ-glutamylcysteine synthetase) promotors that provide *in-vitro* neuroprotection (Kinoshita and Aoyama 2021). Persistent presence of ROS increases cellular oxidative stress and cell death. NF-κB activation causes the expression of pro-inflammatory genes, while Nfr2 activation causes upregulation of stress-inducible genes (Kouvedaki et al. 2024). CDP inhibits ROS and NO generation, protecting the neuronal cells from oxidative stress, as shown in Fig. 4 (Moorthy et al. 2022). Lipopolysaccharides (LPS) are inflammogen which triggers microglial responses leading to the activation of pro-inflammatory mediator which can cause neural damage (Singh et al. 2022).

Systematic *in-vivo* administration of cyclo(His-Pro) exerts anti-inflammatory effects in CNS, preventing LPS neurotoxicity. In LPS activated BV-2 cells endogenous cyclo(His-Pro) inhibits LPS-induced ROS and NO generation, attenuates endoplasmic reticulum stress, reduces microglial inflammation caused by systemic LPS administration, and presides over the Nrf2–NF-κB systems (Wang et al. 2022). Due to the BBB crossing ability, diverse oxidative stress, and inflammatory responses in brain, cyclo(His-Pro) has high potential as therapeutic agent in neuroinflammation-based neurodegenerative pathologies (Mosetti et al. 2022). Cyclo(His-Pro) increases zinc

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absorption (Acun and Kantar, 2024), which shows anti-hyperglycemic activity (Kim et al. 2024) and improved weight loss (Ismael et al. 2024) in both type I and type II diabetes. It improves memory by reducing Aβ-40 and Aβ-42 protein levels in the brain tissues (Afşar and Kantar 2025). *In-vivo* study shows that under basal conditions, zinc administration increases hippocampal neurogenesis by increasing vascular zinc secretion from Paneth cells in the hippocampus. Zinc administration also increases the production of immature neurons in the dentate gyrus and progenitor cell proliferation in the subgranular zone of the hippocampus (Šimončičová et al. 2024). In amyloidogenic APP (amyloid precursor protein) pathway, it can result in the neurotoxic amyloid beta (Aβ) generation, a peptide fragment of Alzheimer's disease (Sajjad et al. 2018). Cyclic *cis*-locked phosphor-dipeptide, cyclized phospho-Thr-Pro (pCDP) derivatives, inhibit the entry of AβPP (amyloid-β precursor protein) into the amyloidogenic processing pathway (Fisher et al. 2017).

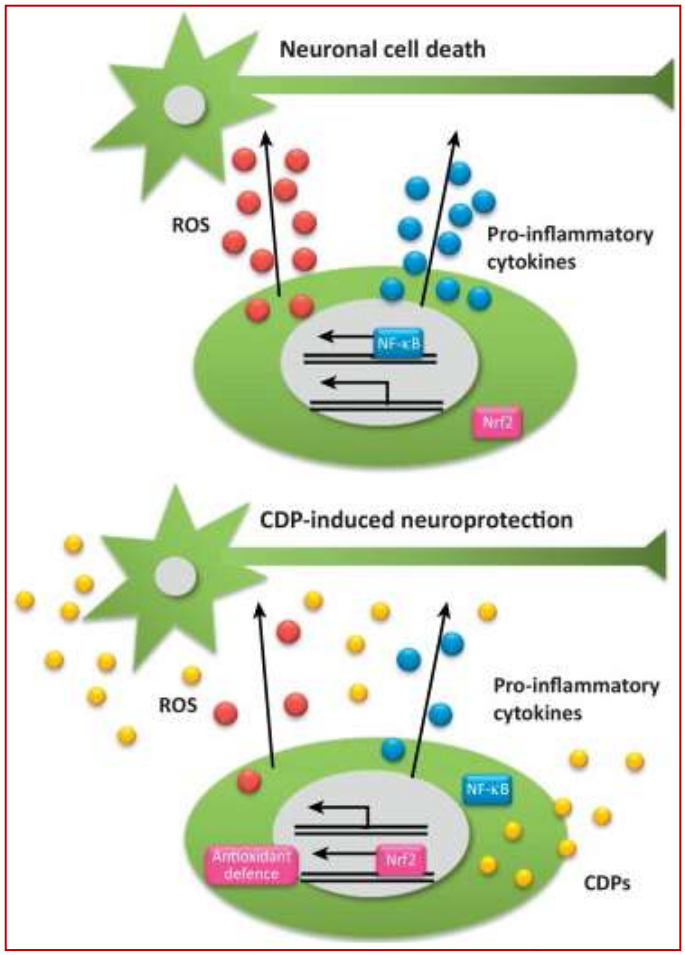

Fig. 4: Neuroprotective role of CDPs (Nrf2–NF-κB systems). Inflammatory mediators acting on microglial cells through NF-κB activation, enhanced generation of cytokines, nitric oxide, and reactive oxygen species, which lead to neuronal cell death. NF-κB activation causes the expression of pro-inflammatory genes while Nfr2 activation causes upregulation of stress-inducible genes. CDP inhibits ROS and NO generation protecting the neuronal cells from oxidative stress. Reprinted from (Moorthy et al. 2022) with permission from Elsevier B.V.

3.2. Anticancer Activity of CDPs

Different types of cancer have afflicted humans from ancient times (Jabbir et al. 2019). The use of high fibrous foods has health improving effects, including the prevention from various chronic diseases. The anticancer drugs, currently available in the market, are not target specific and shown to possess different adverse effects on normal cells. This promotes the discovery of some novel, effective, and nontoxic therapeutic approaches to treat cancers (Sharif et al. 2018). CDPs scaffolds can also be used as novel tools in the development of anticancer therapeutics. *In-vitro* investigation of proline-based CDP showed that cyclo(Phe-Pro) exhibits anticancer activity against three cancer cell lines in humans. It inhibits the growth of MCF-7 (breast), HT-29 (colon) and HeLa (cervical) cells and has potential to induce apoptotic cell death in HT-29 colon cancer cells (Sabernavaei et al. 2024). Cyclo(Tyr-Cys) causes inhibition of cellular proliferation in HT-29 and MCF-7, while cyclo(Gly-Val) was active against HeLa cell lines and HT-29 cell lines. Cyclo(Gly-d-Val) showed anticancer activity against breast carcinomas and cervical carcinomas (Bhukta et al. 2023; Fizza et al. 2025). Moreover, cyclo(L-Leu-L-Pro) from marine bacteria exhibits cytotoxic activity against HEp-2 tumoral cells (Bibi et al. 2020). The same extracted from marine sponges associated with *Pseudomonas fluorescens* strain displayed cytotoxic activity contrary to cancerous Hep-2 cell lines (50% cytotoxic concentration,

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CC_{50} of 207mg^{-1}). However, the toxicity in non-tumoral cells was also reported (Noman et al. 2021). P53 primary tumor suppressor nuclear protein in cells encoded by human gene TP53 induces apoptosis, transient and terminal senescence, contributes towards efficiency and control of DNA repair and recombination, and inhibits tumor angiogenesis (Zhang et al. 2024). P53 is rendered non-functional in most types and almost 50% of human cancers are caused by the mutation or deletion of TP53 gene. In other 50% of tumor cases, where TP53 is not mutated but its pathway is partially incapacitated (Chahat Nainwal et al. 2024). P53 protein levels are tightly regulated in cells by p53 negative regulator E3 ubiquitin ligase MDM2 (human murine double minute 2) and its structural homologue MDM4 helps in ubiquitylating p53 (Chinnam et al. 2022). The MDM2-p53 interactions and reactivation of p53 in tumors that retain wild-type partially inactivated p53, are considered prime therapeutic targets in many anticancer therapies (Peuget et al. 2024)

Cyclo(D-Tyr-D-Phe) induced cytotoxicity in carcinoma A549 cells (IC_{50}: 10µM) through apoptosis without disturbing cell cycle arrest. Cyclo(D-Tyr-D-Phe) affected the release of caspase-3, an important mediator in apoptotic pathway (Fizza et al. 2025). The combined effect of crude CDPs mixture comprising cyclo(L-Pro-L-Val), cyclo(L-Pro-L-Phe), and cyclo(L-Pro-L-Tyr), extracted from PAO1 strain of *Pseudomonas aeruginosa*, mixed in molar ratio 1:1:1 was investigated for anticancer activity in a dose-dependent manner. PAO1-CDPs hybrid promoted apoptosis in HeLa and Caco-2 (colorectal adenocarcinoma) cell lines, with IC_{50} values of 0.53 and 0.66mg/mL, respectively (Bojarska et al. 2021). The aforementioned study indicated that the apoptotic pathway is involved in the apoptosis of cancer cells. The phosphatidylinositol 3-kinase (PI3K) and serine/threonine-protein kinase (Akt) provide a signal transduction network, which is a key regulator of cell growth and survival (Xu and Wu 2021). Protein mTOR belongs to PI3K related kinase family and is a necessary component of PI3K/Akt pathway. PI3K-Akt-mTOR signaling pathway forms a complex network of cell signaling cascade that plays an important role in regulating normal cell functions, such as cell cycle proliferation, cell growth, and protein synthesis. It has high significance in cancer therapeutics, as it is often deregulated in the majority of cancers (Xu et al. 2020). Activation of this pathway results in a profound disturbance in cell growth cycles that ultimately leads to tumor formation (Alzahrani 2019). There are two functionally distinct complexes of mTOR kinase, (i) mTOR complex 1 (mTORC1) and (ii) mTOR complex 2 (mTORC2). The heterotrimeric mTORC1 regulates protein translation, cell growth and differentiation. It is often downregulated in diseased conditions, while mTORC2 regulates Akt *via* phosphorylation on Ser473, protein kinase Cα (PKCα) and insulin signaling cascade.

3.3. Antimicrobial Activities of CDPs

3.3.1. Antiviral Activity of CDPs: *Lactobacillus plantarum* LBP-K10 secretes cis-cyclo(L-Leu-L-Pro) and cis-cyclo(L-Phe-L-Pro) that exhibit high antiviral activity, effectively inhibiting viral cell proliferation and infectivity of influenza A virus (H3N2) (Son et al. 2024). Among various natural and semi-synthetic DKP derivatives from deep-water sediment fungal strain, twelve compounds exhibited excellent activity against *Trypanosoma brucei* (IC_{50}: 0.002-40µM) *causative agent of African sleeping sickness* (Fernández et al. 2024). A novel CDP dimer aspergilazine A from marine-derived fungus *Aspergillus taichungensis* showed weak antiviral activity against H1N1 influenza A virus (Chen et al. 2022). Spiro-diketopiperazine derivative exhibited high antagonistic activity against chemokine receptors, CXCR4 and CCR5. These receptors function as co-receptor for HIV-1 entry into $CD4^+$ cells. These play a critical role in the progression of HIV infection, which is one of the most attractive drug delivery targets in biomedical sciences (Shah and Savjani 2018). *In-vitro* analysis showed that CDP scaffolds 1-butyl-3-(2-methylpropyl)-9-(6-phenylhexyl)-1,4,9-triazaspiro-[5.5]undeca-2,5-dione, 1-butyl-3-(2-methylpropyl)-9-(4-phenoxyphenylmethyl)-1,4,9-tri-azaspiro[5.5]undeca-2,5-dione, and 9-(1,4-benzodioxane-6-yl)-1-butyl-3-cyclohexyl-1,4,9-triazaspiro[5.5]undeca-2,5-dione effectively inhibit the replication of clinical HIV-1 strains as well as potently blocked HIV multidrug resistance variants with minimal cytotoxicity (Nadai et al. 2024).

3.3.2. Antibacterial Activity of CDPs: The inhibitory effect may be due to hydrophobic and cationic nature of CDP that interferes with outer membrane and plasma membrane functions, leading to loss of cellular integrity, ultimately causing cell death (Gowrishankar et al. 2019; Tsai et al. 2020). Cyclo(Leu-Pro) isolated from KH-614 strain showed anti-VRE (vancomycin-resistant enterococci) activity against twelve VRE strains with MIC of 12.5 mg/mL. It was particularly effective against three clinical VRE strains: *E. faecalis* K-00-184, K-00-221, and K-99-34 (Alshaibani et al. 2017). Cyclo(D-Pro-L-Leu) isolated from *Rhabditis* (*Oscheius*) bacterium sp., associated with rhabditid EPN (entomopathogenic nematode) showed good inhibitory activity against four bacterial cultures namely *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli*, while cyclo(L-Pro-L-Leu) and cyclo(D-Pro-L-Tyr) only inhibited Gram-positive bacterial growth (Hirt et al. 2020). Antimicrobial cyclo(L-Tyr-L-Pro), cyclo(L-Leu-L-Pro), cyclo(L-Tyr-L-Pro), and cyclo(L-4-OH-Pro-L-Leu) from a fermentation broth of *Paludifilum halophilum inhibited growth of pathogens E. coli, S. aureus, P. aeruginosa*, *S. enterica, and A. tumefaciens* (Frikha et al. 2017).

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Pathogenicity in *Vibrio cholera* is regulated by ToxR regulon, a regulatory system which controls the production of virulence factors CT (cholera toxin) and TCP (toxin coregulated pilus) in response to external environmental stimuli. The transmembrane protein ToxR senses the external stimulus and activates gene expression of ToxR regulon. It has three internal membrane regulatory proteins: ToxR, TcpP and toxT (Ramamurthy et al. 2020). LeuO a LysR-family DNA binding protein acts as global regulator in pathogens (Islam et al. 2021). In *Vibrio cholerae* O1 El Tor strain N16961 under specific conditions (virulence gene-inducing growth conditions) cyclo(Phe-Pro) shows the ability to obstruct the production of CT and TCP. Its ability to inhibit CT and TCP production is correlated to reduce transcription of TcpPH virulence regulator and is alleviated by TcpPH overexpression (Mey et al. 2024). AphA and AphB are transcriptional regulatory proteins in cytoplasm, and they act as an activator for TcpPH gene expression (Ramamurthy et al. 2020). Antimicrobial CDPs: cyclo(Leu-Pro) and cyclo(Phe-Pro) in culture filtrate from kimchi fermented with *Leuconostoc mesenteroides* and proline-based CDPs, cyclo(Ser-Pro), cyclo(Tyr-Pro), and cyclo(Leu-Pro) from filtrates of CCK (Chinese cabbage kimchi) starter culture, showed significant activity against multidrug resistance bacteria i.e., *S. aureus* 11471, *S. Typhimurium* 12219 strains, Gram-positive, and Gram-negative bacteria (Liu et al. 2017). Complete sets of 16 CDPS, 15 proline-based CDPs and one non-proline CDP produced by *Lactobacillus plantarum* LBP-K10 strain isolated from Korean kimchi, exhibited both individually and in combination remarkable antimicrobial potential against pathogenic fungi, multidrug resistance, Gram-positive and Gram-negative bacteria, and influenza A virus (H3N2) (Kwak et al. 2018).

3.3.3. Antifungal Activity of CDPs: CDPs have shown to possess the ability to kill pathogenic fungi and interfere with their growth (Ma et al. 2024). Several naturally produced and synthetic groups of CDPs are considered as promising antifungal agents showing broad-spectrum bioactivities. Fellutanine [cyclo(Trp-Trp)] from *Penicillium* sp., (strain KF620) showed antimicrobial activity against *Candida glabrata* and *Xanthomonas campestris* (Cochereau et al. 2023). *Chryseobacterium* sp., cyclo(4-OH-Pro-Leu) and cyclo(Pro-Leu) function synergistically demonstrating strong algicidal activities against dominant bloom-forming cyanobacterium, *Microcystis aeruginosa*. Cyclo(4-OH-Pro-Leu) enhances intracellular ROS levels, decreases anti-oxidase activity, interrupts electron transport flux, while cyclo(Phe-Leu) inhibits intracellular antioxidant activity (Van Le et al. 2023). CDPs are isolated from bacterium *Achromobacter xylosoxidans* effect aflatoxin production in *Aspergillus parasiticus* and inhibit fungal growth at high concentration (>6.0mg/mL) (Kang and Kwak 2023). *Ralstonia solanacearum* causes bacterial wilt in crops and other agricultural problems worldwide. Bioactive cyclo(L-Pro-D-Ile) and cyclo(L-Pro-L-Phe) from *E. coli* GZ-34 downregulated the expression of pathogenicity contributor (hrpB, pilQ, cellulase encoding gene, phcA, epsF, fliT, pilQ, cheW) of *R. solanaecearum*. Cyclo(L-Pro-L-Phe) also prevented spore formation in *Magnaporthe grisea* (Song et al. 2018).

4. CONCLUSION

Several CDPs have been identified in the plant and animal kingdoms, including marine sponges and fungi. Cyclo(His-Pro) is the only CDP that has its confirmed origin in mammals. CDPs have been identified in hydrolysates of proteins and polypeptides, as well as in fermentation broths and cultures of lichens, yeasts, and fungi. CDPs exhibit various important physiological advantages due to the presence of cyclic constraints, as they have demonstrated higher resistance to enzymatic degradation and greater stability than their linear counterparts. They can also cross different physiological barriers, and the limited conformational freedom provides a bioactive conformation, which improves receptor site selectivity and pharmacological specificity. Linear dipeptides and CDPs/DKPs are present in great amounts in nature and produced by a variety of organisms, including bacteria, yeast, marine fungi, plants, Cucurbitaceae, and Orchidaceae families of plants, and various mammals, including humans. The non-ribosomal synthesis of CDPs has also been found to be catalyzed by a new class of enzymes (cyclodipeptide synthases). Non-ribosomal peptide synthases are modular and multifunctional mega-enzymes. They have long been considered for non-ribosomal synthesis of CDPs and macrocyclic compounds. In addition to NRPSs, another class of small enzymes (cyclodipeptide synthases) has also been discovered, which is involved in catalyzing the production of CDPs during the albonoursin synthesis pathway. These enzymes utilize aminoacyl-tRNAs (aa-tRNAs) as substrates to catalyze the formation of two peptide bonds without the need for ATP, resulting in the production of a cyclic dipeptide through the sequential ping-pong mechanism. CDPs can also be synthesized chemically from their linear counterparts in solution and solid phases. The synthesis of the solution phase of CDPs is generally carried out through the mixing of triethylamine and diethyl-phosphoryl cyanide with the stirred solution of N-t-Boc-L-X(a.a) and L-X(a.a)-OMe in 1,2-dimethoxyethane. As a novel class of biomolecules, CDPs influence quorum sensing (QS) signaling. The role of CDPs as QS mediators is not fully recognized yet. The molecules of microbial QS can reduce host innate immune responses towards viral infection through an inter-kingdom network of pathogen cross-talks between host and viruses or bacteria. CDPs can also affect the formation of biofilm in various microorganisms, as the formation of biofilm in different bacteria is regulated by QS process and CDPs show QS quenching activities. An increasing number of CDPs

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have been identified for various important biological activities, including antiviral, antibacterial, antifungal, antihypertensive, antioxidant, antihyperglycemic, antitumor, antiarrhythmic, neuroprotective, nootropic, cytoprotective, quorum sensing, chitinase inhibition, alteration of blood clotting functions, and analgesic properties. Different proline-based CDPs with biological activities have been found in different beverages and processed foods. Many biologically active peptides interact with multiple receptors, and constraining specific structural features can lead to drugs with fewer or no adverse effects and high receptor specificity. Therefore, the study of synthesis and constrained analogues has evolved as a powerful approach in peptide drug design. Moreover, cyclopeptides have been well recognized for their biological importance, including their roles as toxins, hormones, antibiotics, and ion-transport regulators. The biological diversity and properties of the cyclic dipeptides have been reviewed, but comparatively little is known about any further functions in the producing organisms. To fully understand the exact role of these CDPs in nature, further studies are needed in the future. We hope that this review article will provide more attention towards these amazing and versatile molecules in the future and will help to reveal more about their importance, functions, and role in nature.

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Data Availability: All data are available within the article.

Ethics Statement: This is a review article. We, the authors, have honestly collected the published literature about the subject and did not conceal any facts.

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