Applied Chemical Engineering (2023) Volume 6 Issue 1
doi:10.24294/ace.v6i1.1989

REVIEW ARTICLE

Recent advances in self-assembled cyclic peptide-based smart nanostructures

Monika Kherwal[1], Akanksha Gupta[2], Mercykutty Jacob[2], Anshuman Chandra[1], Prasanta Kumar Sahu[3], Vijay Kumar Goel[1*], Vinod Kumar[4*]

[1] *School of Physical Sciences, Jawaharlal Nehru University, Delhi 110067, India. E-mail: vijaykgoel@mail.jnu.ac.in*
[2] *Department of Chemistry, Sri Venkateshwara College, University of Delhi, Delhi 110021, India.*
[3] *Department of Chemistry, Shivaji College, University of Delhi, Delhi 110027, India.*
[4] *Special Centre for Nano Science, Jawaharlal Nehru University, Delhi 110067, India. E-mail: kumarv@mail.jnu.ac.in*

ABSTRACT

Peptide chemistry has emerged as one of the growing fields of research. Peptide chemistry has positively impacted various areas, including biochemistry, medicine, hormonal therapy, drug delivery, food and the cosmetic industry, materials science, and nanotechnology, via the development of ways to change and imitate the shape and function of peptide structures. The structural changes of peptides and the employment of innovative synthetic techniques have left an indelible mark on a number of scientific disciplines. Numerous nanostructures based on simple and complicated peptides have been constructed so far; however, cyclic peptides have attracted a great deal of interest from the scientific community due to their wide range of applications and distinctive properties. These properties include self-assembly, morphogenesis, and charge distribution, among others. In addition, nanostructured cyclic peptides offer increased and effective performance due to their high stability, prolonged plasma half-life, membrane permeability, and efficient transport, among other attributes. Recent work indicates the manufacture of nanostructured cyclic peptides by chemical means. In this review, a brief investigation of the morphology of cyclic peptides was conducted. In addition, the therapeutic potential of these nanostructured cyclic peptides and the prognosis for a variety of potential applications are also discussed.

Keywords: Peptides; Cyclic Peptides; Therapeutic; Nanotubes; Nanowires; Nanospheres; Drug Delivery

ARTICLE INFO

Received: 14 March 2023
Accepted: 24 May 2023
Available online: 24 July 2023

1. Introduction

The human body is composed of proteins with monomeric units of amino acids[1]. Peptides are biopolymers made-up of long chains of amino acids held together by amide bonds. They are a vital component of the human body and conduct a wide range of biological functions. Because both peptides and proteins are composed of amino acids, the body readily accepts peptides. Both peptide chemistry and nanotechnology are highly advanced and the relevant research fields are gaining widespread awareness nowadays. Today, research in these areas is of the utmost importance for the progress of sophisticated and efficient medication delivery mechanisms. Peptides are utilized as promising biomaterials for disease diagnostics[2]. Peptides can attach to specific targets, such as those present within cancers tissues, bones, muscles, and other human tissues. Due to their short plasma half-life and propensity to be proteolyzed and eliminated from the body[3], peptides have limited clinical applicability. As opposed to linear peptides, cyclic peptides are invulnerable to proteolytic degradation and have a longer half-life due to their more resilient molecular arrangement constraints[4]. As a result of their multiple properties, such as bi-

odegradability, biocompatibility, and bioactivity, these biomolecules are likely to perform a variety of biological functions or activities and form complex biological material[5]. Cyclic peptides exhibit intramolecular hydrogen bonding[6], reduced peptide polarity and increased membrane permeability[7]. Nanostructured cyclic peptides (NCPs) possess stratified superstructures and desirable biological properties, hence enhancing therapeutic efficacy, targetability, and blood circulation time. Self-assembling NCPs are more stable and effective than native peptides in targeting processes and medicinal applications[8]. Supramolecular self-assembly of peptides and nanomaterials is regarded as one of the most advantageous techniques for the formation of very stable peptide-based nanostructures[9,10]. Cyclic peptide nanoparticles may be well utilised in drug delivery systems[11,12], biosensors[13,14] and drug regeneration[15].

Nanocarriers' physiochemical characteristics are notoriously difficult to alter, however self-assembled nano-based peptides can be easily modified with functional groups to alter their biological activity[16]. These can be generated using a straightforward technique known as solid-phase peptide synthesis and purified using normal HPLC[16]. Peptide-based nanostructures are constructed using a variety of interactions, including electrostatic connections, stacking, and hydrogen bonding[17]. **Figure 1** depicts several peptide self-assemblies, including hydrogels, nanotubes, nanospheres, nanowires, and nanogels[18]. Peptides are organised into nanostructures with diverse interactions.

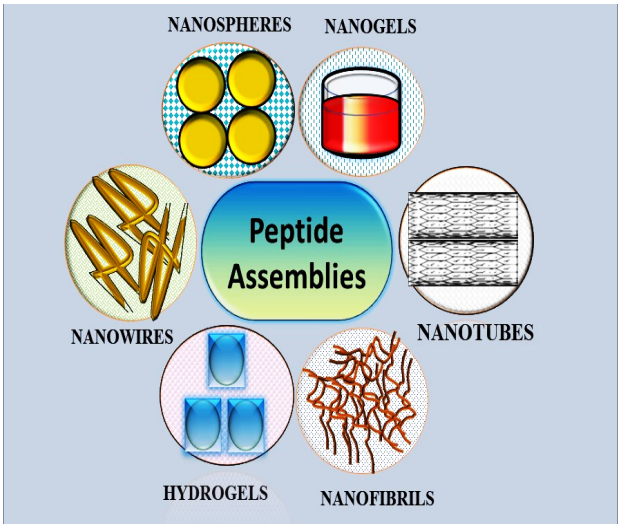


Figure 1. Self-assembled nanostructures of cyclic peptides.

2. Synthesis of cyclic peptides

Cyclic peptides are polypeptide chains containing amino acids arranged in a circular or ring-like structure[19]. In comparison to linear peptides, they are more stiff and proteolytically stable. **Figure 2** demonstrates the various categories of cyclic peptides which are classified into groups[20]. Head represents amine group of peptides and tail represents carboxylic group. Cyclic peptide is generated by linking an amine functional group to a carboxylic functional group from one end to the other. These peptides have intramolecular hydrogen bonding or π-π stacking which is responsible for their self-assembly[17–20].

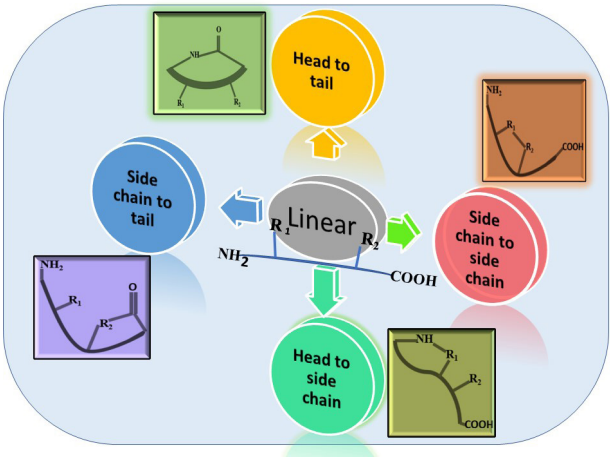


Figure 2. Different types of methods for cyclization of linear peptides, i) R_1 = Amino acid 1 and R_2 = Amino acid 2, vary according to different amino acid side chains.

Mandal *et al.*[21] published the synthesis of a cyclic octapeptide $[WR]_4$. The synthetic process comprises solid-phase synthesis using Arg(pbf)-2-chlorotrityl resin (1 equiv.) swollen in DMF under an atmosphere of nitrogen. In the presence of DIPEA, Fmoc-Trp(Boc)-OH (2 equiv.) and Fmoc-Arg(pbf)-OH (2 equiv.) were alternately loaded (4 equiv.). For elimination of N-terminal Fmoc, a solution of piperidine (20% v/v) was utilised. Using a combination of TFE/acetic acid/CH_2Cl_2 (2:2:6 v/v/v) for 2 h, the whole peptide chain was isolated from the resin without eliminating the side chain protections. The cyclization of the resin-cleaved and side chain-protected peptide was carried out using DIC (1.5 equiv.) and HOAT (1.5 equiv.) in dry DMF/DCM (2:1% v/v) for 12 h with continual stirring in a nitrogen environment. The side chain protections of the cyclized peptide were removed by treating it with a combination of TFA/thioanisole/

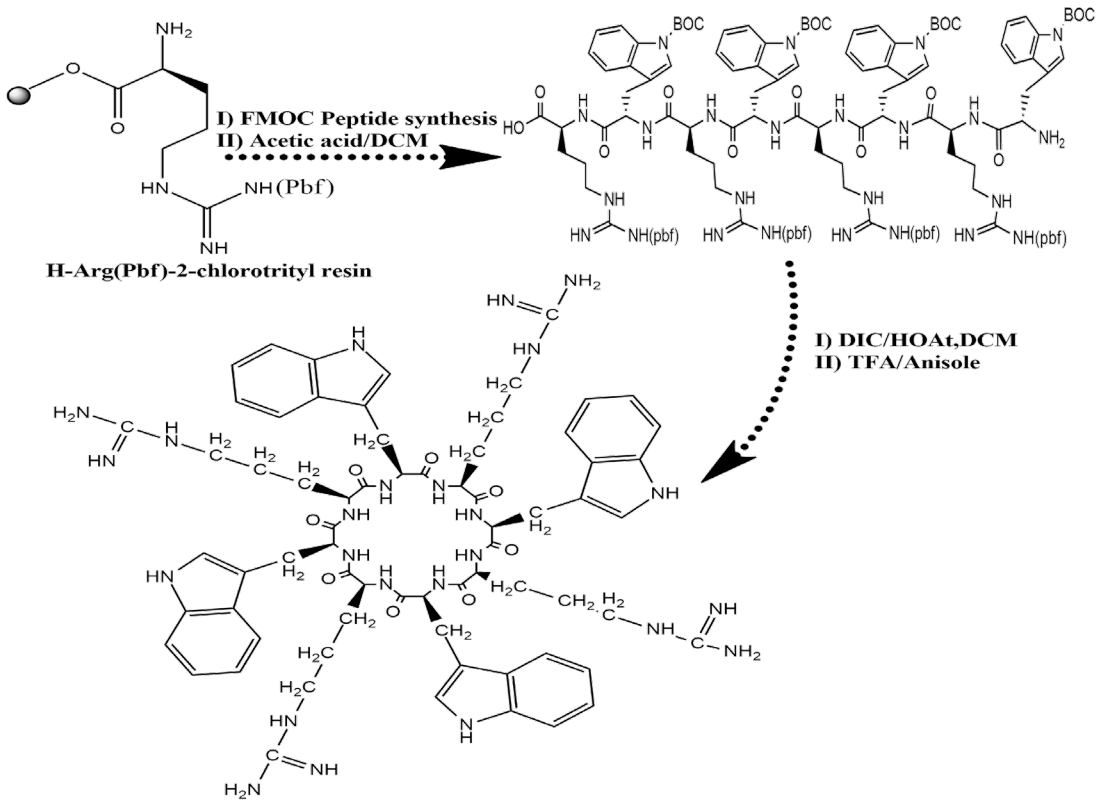


Figure 3. Solid-phase peptide synthesis of $[WR]_4$.

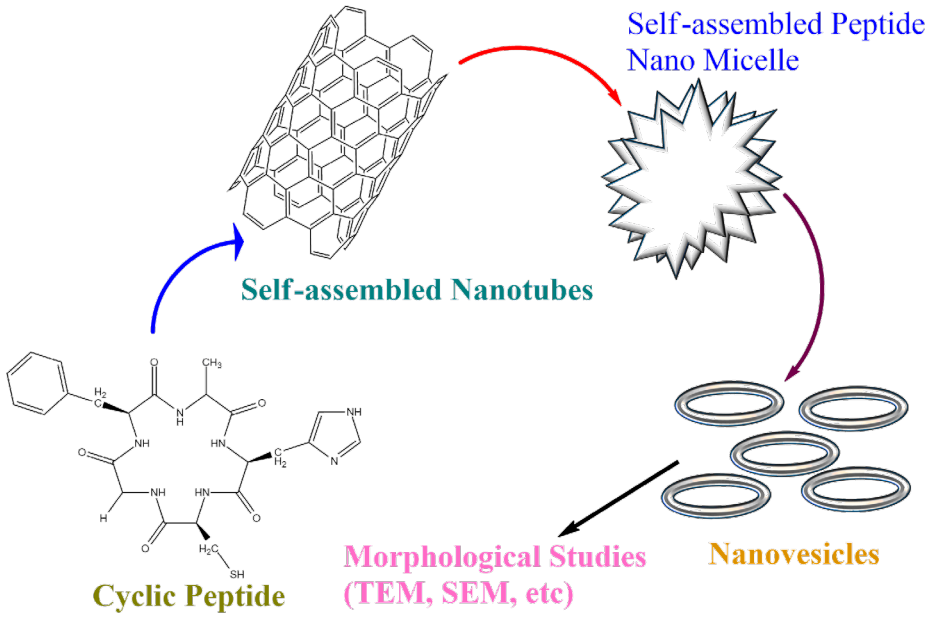


Figure 4. Mechanism of self-assembled nanostructure of cyclic peptide.

anisole/EDT (90:5:2:3, v/v/v/v) for 2 h, followed by precipitation in precooled diethyl ether. They synthesized many other cyclic peptides, one of them is $[WR]_4$ which has been illustrated in **Figure 3**.

2.1 Nanospheres

Nanospheres are a class of nanoparticles having the size of a few nanometres and of spherical shape. For their synthesis, initially cyclic peptides were synthesized by Mandal *et al.*[21], they have done the selection of amino acid residues based on the hydrophobic nature and charged nature. Cyclic peptides do not show cytotoxicity. Now, for self-assembly of cyclic peptides, 2 mm solution was produced using distilled water and incubated for 48 h at room temperature. To analyse the nanostructure formation, different analytical techniques were used for characterization of peptide solution. Oth-

er characterizations were done by TEM, FESEM, AFM. Panigrahi *et al*.[22] synthesized different kinds of cyclic peptide nanospheres which were found to have a size of approximately 400 nm. Here, in this work, initially nanotubes were prepared which later on converted to nanospheres. As depicted in **Figure 4**, a cyclic peptide undergoes a self-assembling mechanism. Subsequently, they are converted into nanotubes, followed by conversion into nanosphere or vesicles. Nanotubes, nanowires and nanospheres are interconvertible to each other.

Kumar *et al*.[23] prepared Tryptocidine C (TpcC), rich in Trp amino acid having cyclodecapeptide. This has high inclination to oligomerize in solution and its dried form attains different self-assembled nanostructures. Its nanospheres have a diameter of around 24.3 nm. **Figure 5** illustrates Tryptocidine C self-assembled into nanospheres with various types of interactions[23].

2.2 Nanotubes

Cyclic peptides were prepared via the process of solid-phase peptide synthesis. Glu and Lys amino acids were used to form nanotubes because they attain antiparallel β-sheet type interactions in long chain[24,25]. The visualization of nanotubes was done on mica surface, the mixture of peptide and ACN/H_2O (3:2) were settled down on mica surface for 1 h. Now, the surface was cleaned using Milli-Q water then the obtained sample was dried. AFM topographic analysis helped in finding the size of nanotubes to be ~2.4 nm[26].

Figure 6 shows hydrogen bonds between peptide backbone functions and stacking interactions with pyrene moieties which assist in self-assembly and nanotubes deposition over mica surface. Consequently, this is followed by covalent bond hydrolysis which accelerates the removal of pyrene moieties. Nanotubes produced via this process were of size 2.2–2.6 nm[26].

Katouzian *et al*.[27] synthesized nanotubes from cyclic peptides by using different types of methods. However, Ghadiri and co-workers were the first to carry out synthesis of nanotubes of cyclic peptides[28]. They concluded that peptides form β-turns which stack over each other making a hollow nanocylinder. The obtained nanotubes from cyclic peptides were found to be of diameter 7–8 Å. **Figure 7** and **Figure 8** show different setups for formation of nanotubes of given sample peptides or proteins. In pulse electric field process, pump was used through which peptide gets inserted, undergoes treatment chamber connected to a high voltage generator and produces nanotubes. While, by Template-based layer by layer deposition process, layers were formed over one another, absorbed on a surface and after mixing with specific solvent, peptide layer gets converted to nanotubes[27]. Also, the nanotubes' capacity was analyzed to transfer or hold tiny compounds selectively[29,30].

Suris-Valls *et al*.[31] prepared nanotubes from cyclic peptides and applied in inhibition of ice recrystallization, persuaded by the achievements of Ghadiri *et al*.[28]. They synthesized staggered forms such as L and D-amino acids octapeptide named Lys2CP8 by inducing π-π stacking of cyclic peptides into antiparallel β-sheets[28].

The linear peptide prepared via solid-phase peptide synthesis was taken into RB (round bottom) flask using septum, which was purged with argon

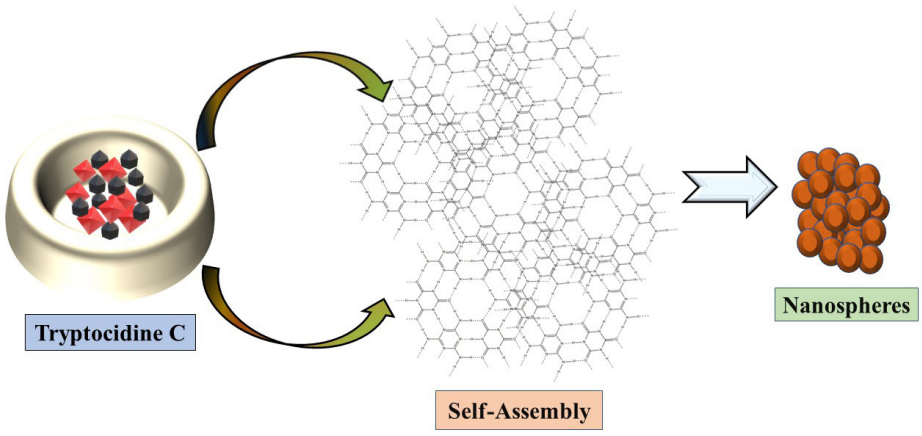
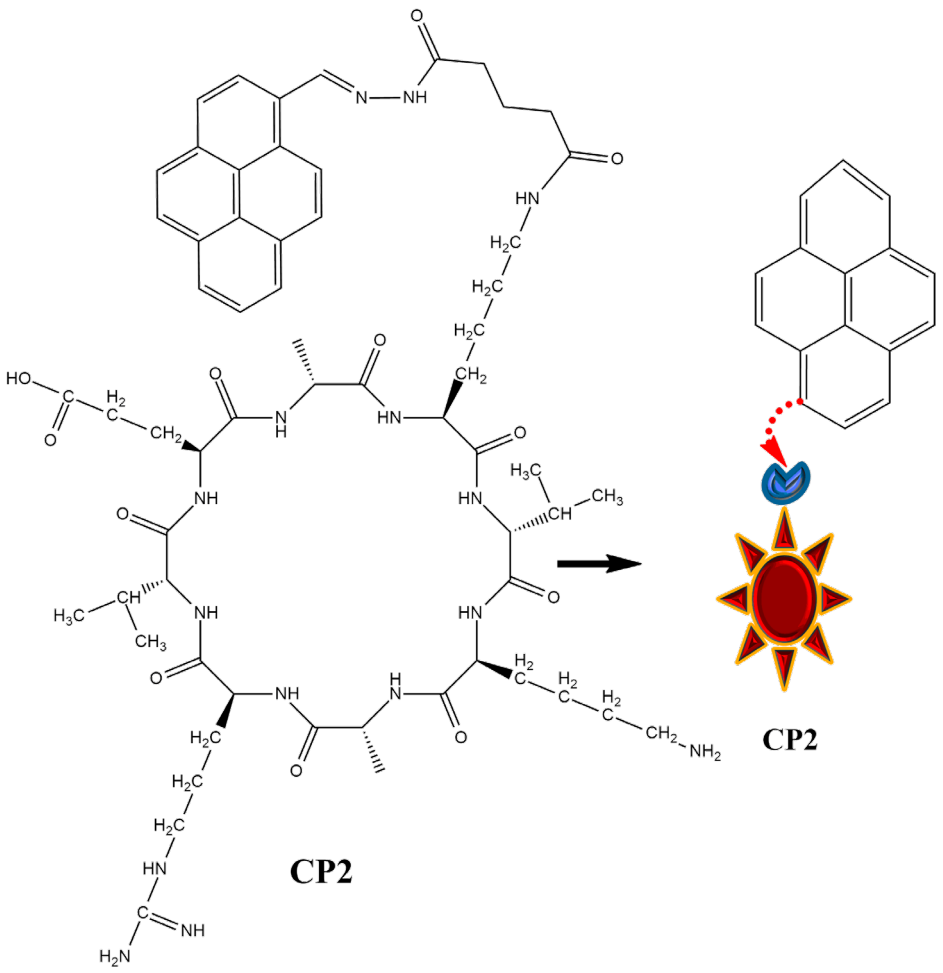
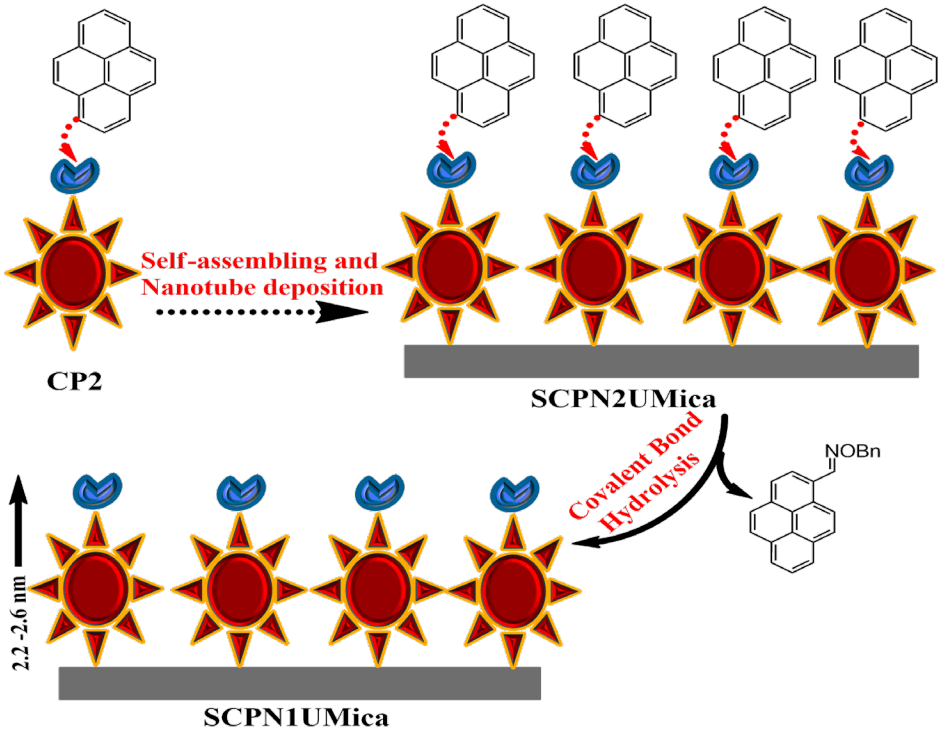


Figure 5. Systematic diagram of self-assembly (nanospheres) of Tryptocidine C.



(a)



(b)

Figure 6. (a) Pyrene moiety incorporated with cyclic peptide 2 and its description via a ring. (b) Formation of nanotubes from self-assembly of pyrene moiety with cyclic peptide, CP2 = cyclic peptide 2, SCPN2UMica = self-assembled cyclic peptide nanotubes 2 on mica surface, SCPN1UMica = self-assembled cyclic peptide nanotubes 1 on mica surface.

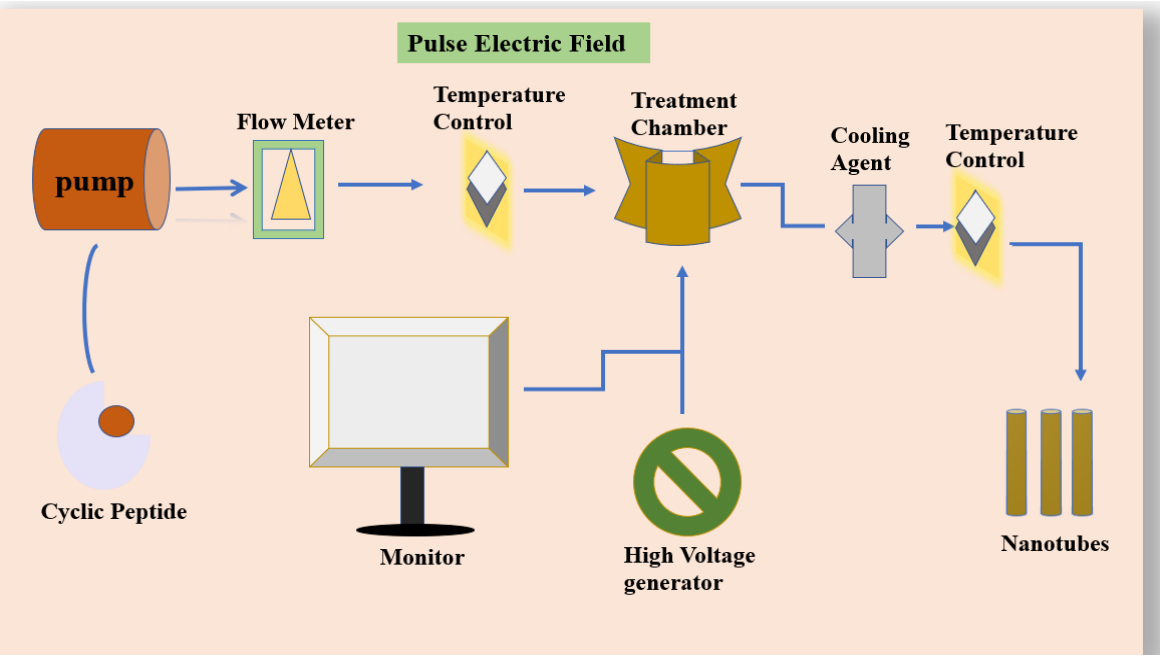


Figure 7. Pulse electric field method or setup for formation of nanopeptides from cyclic peptides.

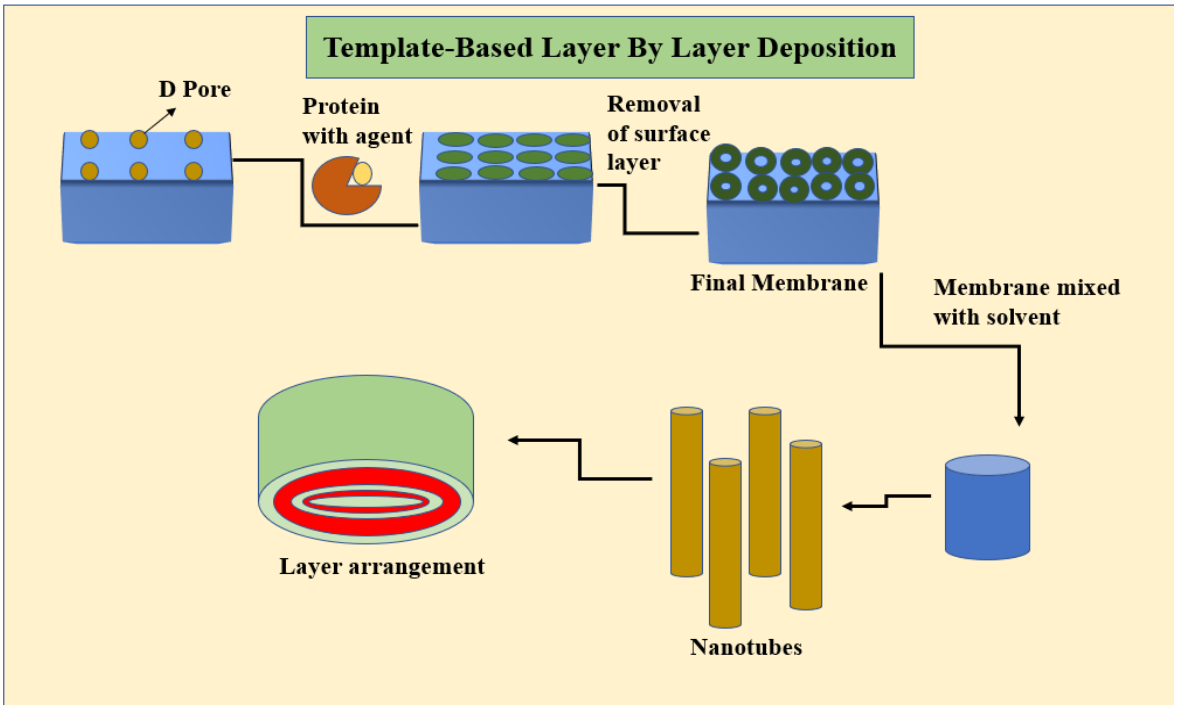


Figure 8. Template-based layer by layer deposition methods for formation of protein nanotubes.

and then the linear peptide was dissolved in DMF. DMTMM·BF_4 and added to the above solution, then stirred magnetically in presence of argon pressure overnight. Washing of sample was done with deionized water, the sample was purified and dried. Then obtained cyclic peptide underwent self-assembly or scaffold creation for formation of nanotubes[31]. The obtained nanotubes of this cyclic peptide were of size 200 nm. Ghadiri *et al.*[28] showed that the cyclic closed rings stack into nanotubes via hydrogen bonds and form dihedral β-type angles. **Figure 9** shows structure of cyclic peptide Lys2CP8[31].

2.3 Nanowires

Self-assembly is a pervasive and very attractive strategy for fabricating nanomaterials. There are two types of nanostructures formed by cyclic peptides. One of them is D,L-cyclic system, produced by Ghadiri *et al.* in 1993[28]. This type of cyclic peptide foregathers within empty tubes through

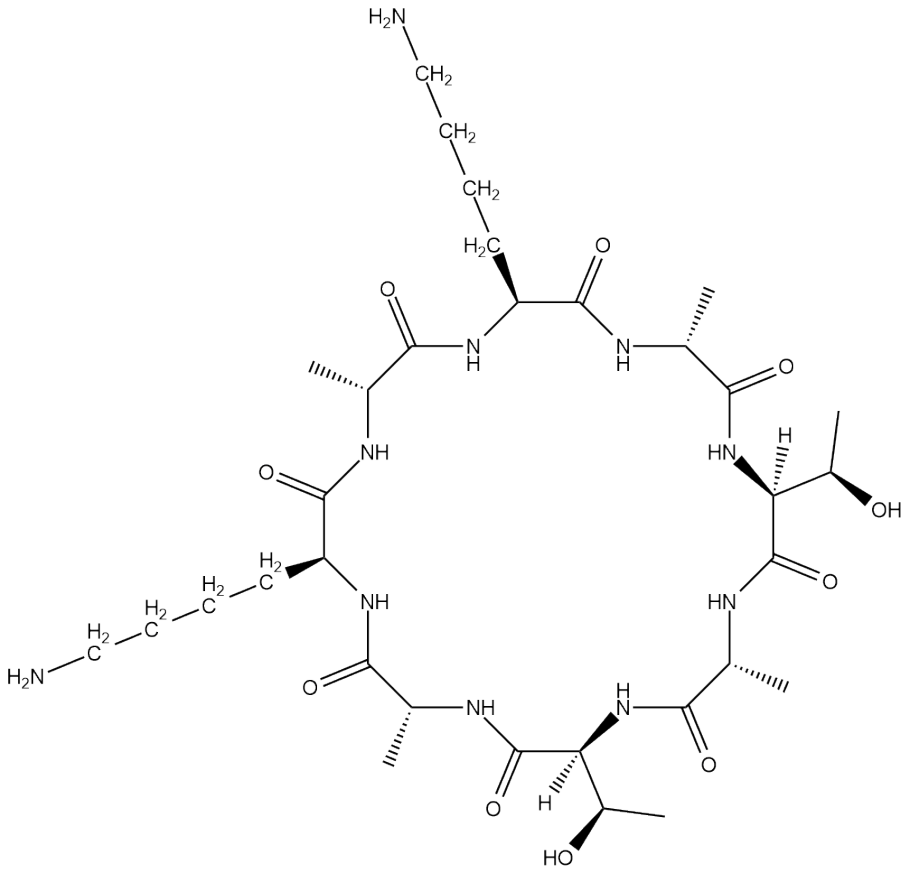


Figure 9. Synthesized cyclic peptide.

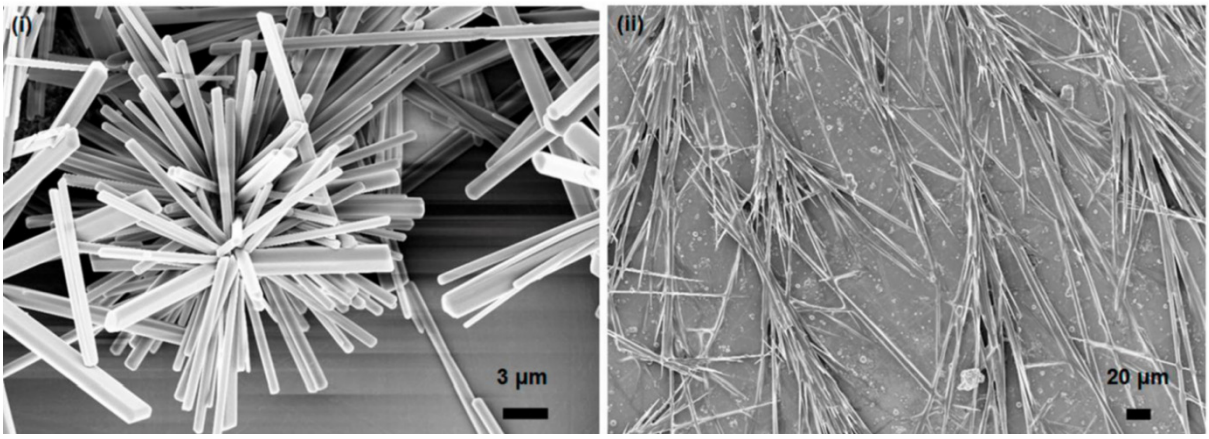


Figure 10. SEM images of self-assemblies of peptides into nanorod-like structures. Reproduced from [32]. Copyright © 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

stacking. These cyclic peptides are associated with different advantages, like flexible external functionalities and internal diameter. These pipe-like structures are used as antibacterial agents, in molecular electronics and in ion channels. Konda *et al.*[32] synthesized modulated self-assembled hydrogen-bonded tripeptides forming nanorods. **Figure 10** shows the self-assembly of peptides transformed into nanorods having a width of 3 µm and the length of around 20 µm[32].

Zhao *et al.*[33] synthesized nanowires from Diketopiperazines which are the smallest cyclic peptides found in bacteria and human beings. Cyclic dipeptides were synthesized via solid-phase peptide synthesis completed with cleavage induced cyclization of linear dipeptide. These cyclic diketopiperazines rings have several bonding connections like covalent, intramolecular hydrogen bonding and π-π stacking which are responsible for self-assembly. These cyclic peptides are self-assembled into various nanostructures, and nanowires are one of them. In this paper, nanowires obtained were

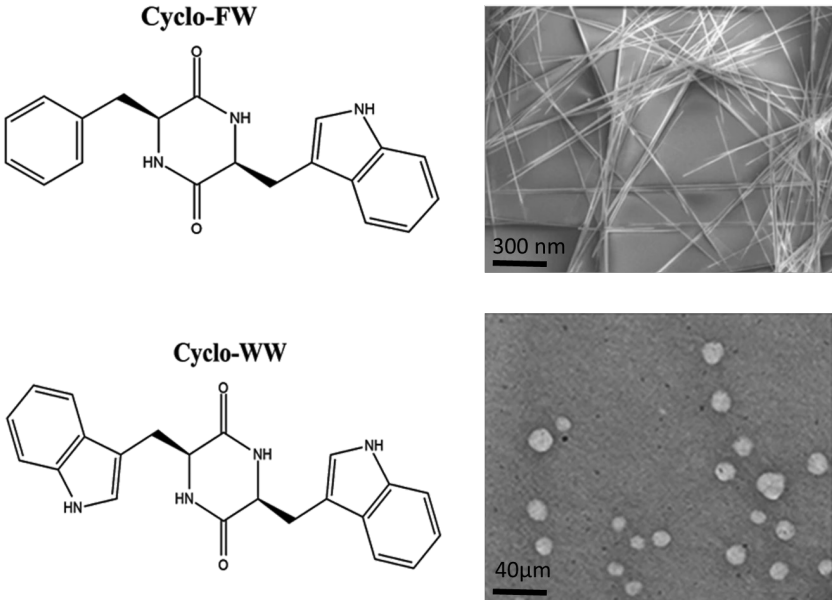


Figure 11. SEM images of two different cyclic dipeptides. Reproduced with permission from [34].Copyright © 2018, The Author(s).

Table 1. Cyclic peptide-based nanostructures and their particle sizes

Cyclic peptides-based nanostructures	Sizes of particles	Bonding interactions	Reference
Nanospheres	400 nm 24.3 nm	Hydrogen bonding (intramolecular)	[21], [23]
Nanotubes	2.4 nm 7–8 Å	π-π stacking interactions	[26], [27]
Nanowires	40 µm, 300 nm	π-π stacking, hydrogen bonding	[33]

of size 40 µm for cyclo-FW peptide and 300 nm for cyclo-WW peptide. **Figure 11** shows two cyclo-peptides transformed into nanowires of different sizes[33].

3. Applications of nanostructured cyclic peptides

NCPs have emerged as versatile materials in various applications due to their proteolytic stability, hydrophobicity, charge, stability and ease of self-assembly formation[35]. Current research trends have seen a rise in the usage of NCPs in therapeutic applications, imaging, food industry, cosmetics and pharmaceuticals. Some of these important applications have been further discussed briefly in the following section.

Fluorescent cyclic peptides (FCP) have scaffolds that act as optical agents for cell imaging[36]. FCP focuses on biological target receptors that have high proportions in tumour tissues. The cyclic peptide (WXEAAYQKFL) was coupled with a carboxyfluorescein next to the NH_2 group of the D-lysine residue side chain. FCP has a great advantage of detecting breast cancer cells in human blood. The other derivatives of this cyclic peptide convey advantages as theranostic probes linked with chemotherapeutic drugs, which increases its target efficacy. These types of peptides targeting cell receptors as oxytocin receptors have an important role in reproductive system; for detection Nile Red dye and a PEG spacer were used to produce activated fluorescent probe with upgraded abilities for oxytocin imaging[37]. In vivo imaging applications of FCP with different probes and also real-time intraoperative tumour detection in liver and lung of mouse model was analyzed by Tapia *et al*.[37].

Probe I illustrates zwitterionic form of molecule to balance its charge. These different near-infrared (NIR) fluorescent probes were introduced before 4 h of imaging within each mouse veins.

Cyclic peptides are permeable to plasma membranes via passive diffusion due to their hydrophobic residues. These molecules bind with cell surface protein transporters which directly haul them to cells[38]. Cell penetrating property of cyclic peptides emerged as boon to therapeutic industry and in cell imaging. **Table 2** illustrates various cyclic peptides and their applications or activities based on tested organisms. There are further diversification and ap-

Table 2. Cyclic peptides and their applications

Cyclic peptides	Applications	Remarks	Reference
Enterocin AS–48	Vegetable food preservation or beverage preservation	This cyclic peptide derived from enterococcus bacteria	[39]
WXEAAYQKFL	Tumour cell imaging	Observed on human breast cancer cells	[37]
Lactocyclicin Q	Antimicrobial activity	Animals like cow, buffalo (derived from cheese)	[40]
Uberolysin	Anti-bacterial activity	Tested organisms *Streptococcus uberis* (lips and skin of cows)	[40]
Cycloviolacin O2 Cyclopsychotride A Kalata B1, Kalata B2	Anti-microbial activity	Tested species *Pseudomonas aeruginosa*, *E. Coli*, *S. aureus*	[41], [42]
Cycloviolacin O2	Anti-cancer	MCF–7 species tested for anti-cancer activity	[43]
Ribifolin Curcacycline B Chevalierin A	Anti-malarial	*Plasmodium falciparum* tested species for anti-malarial activity	[44], [45]
Kalata B1 Kalata B7	Uterotonic	Application observed for human myometrium extract	[41]

Table 3. Food diversification based on different sources and their applications

Proteins	Sources	Applications	Reference
Keratin	Sweet potato, garlic, mango, salmon	Helps in tissues of hair, nails and in lining of skin	[51]
Casein	Milk, eggs	Building of muscles	[52]
Actin	Fish, meat	Cell motility Muscle contraction Cell signalling	[53]

plications of other cyclic peptides.

Antimicrobial activity is one of the important applications of nanomaterials of cyclic peptides, delivery of drugs becomes effortless with the nanomaterials, they enhance stability and bioavailability. Antimicrobial peptides are dragging attention nowadays in place of conventional antibiotics[46–48]. Antimicrobial peptides are attached to the surface of porters to be delivered. These peptides are used as adjuvants in cancer chemotherapy[4]. These were also applicable in delivery of nucleic acids since they exhibit large proportions with NH_3^+ amino acid residues like lysine, histidine and arginine which bind with COO^- nucleic acids very efficiently. Antibacterial photodynamic therapy turns up as a better treatment of bacteria without persuading remarkable resistance to drugs[49].

Wang *et al*.[4] highlighted that food ingredients have forged with materials science and engineering fundamentals associated with various applications. Food classifications are huge, biocompatible, biodegradable and economical to produce novel food ingredients. pH-cycle is a green and facile passage to generate self-assembled nanostructures. There are many types of bacteriocins having variety of applications in food industry[50].

Sulthana and Archer[50] elaborately reviewed several bacteriocins which are applicable in food preservation from various researches. For instance, pediocin as gold nanoparticles with adhesion protein and nisin as carbohydrate nanoparticle have applications in food preservation.

Abriouel *et al*.[39] illustrated vegetable food preservation and beverage applications using cyclic peptide Enterocin AS–48. This bacteriocin also shows antimicrobial activities. Peptides constitute proteins which in turn can be outsourced from various food sources. **Table 3** lists the numerous proteins and the multiple application in food diversification.

4. Conclusion

The cyclic peptides themselves have many remarkable applications due to their proteolytic stability and constrained architectures. Cyclic peptides when turned into nanoparticles, their usefulness is substantially enhanced. The uses of these nanomaterials vary due to their distinct morphologies. Structural morphologies of all of these nanomaterials can be converted into one another under certain conditions. Applications of cyclic peptide nanotubes in the food sector, pharmaceuticals, cosmetics, and cell imaging are expanding quickly. This review discusses the detailed study of the synthesis, design, and bonding interactions of cyclic peptide-based self-assembled nanomaterials, including stacking,

hydrogen bonds, and covalent interactions. These nano vehicles save time and money and pave the way for the most effective treatments for a variety of diseases, and also have applications in the food industry as preservatives.

Acknowledgments

One of the authors Monika thanks Council of Scientific & Industrial Research (File no. 09/0263(15268)/2022-EMR-I) for Junior Research Fellowship. Author Vijay Kumar Goel would like to thank Sanganeria Foundation for financial support. The authors also show gratitude to AIRF, JNU (India), SPS, and SCNS JNU (India) for instrumentation facilities.

Conflict of interest

The authors affirm that there is no conflict of interest to disclose.

Abbreviations

AFM = Atomic field microscopy
DIC = N,N'-diisopropylcarbodiimide
DIPEA = N,N-diisopropylethylamine
DMF = N,N-dimethylformamide
DMTMM·BF4 = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate
EDT = 1,2-ethanedithiol
FESEM = Field emission scanning electron microscopy
Fmoc = N-(9-fluorenyl) methoxycarbonyl
H-Arg(pbf)-2-chlorotrityl resin = Ng-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginine-2-chlorotrityl resin
HBTU = 2-(1H−Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAt = 1-hydroxy-7-azabenzotriazole
HPLC = High-performance liquid chromatography
TFA = Trifluoroacetic acid
TFE = Trifluoroethanol

References

1. Demmer O, Dijkgraaf I, Schottelius M, *et al*. Introduction of functional groups into peptides via n-alkylation. Organic Letters 2008; 10: 2015–2018. doi: 10.1021/ol800654n.
2. Valeur E, Guéret SM, Adihou H, *et al*. New modalities for challenging targets in drug discovery. Angewandte Chemie International Edition 2017; 56(35): 10294–10323. doi: 10.1002/anie.201611914.
3. Qi G, Gao Y, Wang L, Wang H. Self-assembled peptide-based nanomaterials for biomedical imaging and therapy. Advanced Materials 2018; 30(22): e1703444. doi: 10.1002/adma.201703444.
4. Wang C, Hong T, Cui P, *et al*. Antimicrobial peptides towards clinical application: Delivery and formulation. Advanced Drug Delivery Reviews 2021; 175: 113818. doi: 10.1016/j.addr.2021.05.028.
5. Sharma R, Borah SJ, Bhawna, *et al*. Functionalized peptide-based nanoparticles for targeted cancer nanotherapeutics: A state-of-the-art review. ACS Omega 2022; 7(41): 36092–36107. doi: 10.1021/acsomega.2c03974.
6. Moore TS, Winmill TF. CLXXVII.—The state of amines in aqueous solution. Journal of the Chemical Society, Transactions 1912; 101: 1635–1676. doi: 10.1039/CT9120101635.
7. Buckton LK, Rahimi MN, McAlpine SR. Cyclic peptides as drugs for intracellular targets: The next frontier in peptide therapeutic development. Chemistry—A European Journal 2021; 27(5): 1487–1513. doi: 10.1002/chem.201905385.
8. Abdullah T, Bhatt K, Eggermont LJ, *et al*. Supramolecular self-assembled peptide-based vaccines: Current state and future perspectives. Frontiers in Chemistry 2020; 8: 598160. doi: 10.3389/fchem.2020.598160.
9. Sato K, Hendricks MP, Palmer LC, Stupp SI. Peptide supramolecular materials for therapeutics. Chemical Society Reviews 2018; 47: 7539–7551. doi: 10.1039/c7cs00735c.
10. McLaughlin CK, Hamblin GD, Sleiman HF. Supramolecular DNA assembly. Chemical Society Reviews 2011; 40: 5647–5656. doi: 10.1039/c1cs15253j.
11. Sharma R, Gupta A, Kumar R, *et al*. An update on COVID-19: Role of nanotechnology in vaccine development. SMC Bulletin 2020; 11: 88–96.
12. Tran S, DeGiovanni PJ, Piel B, Rai P. Cancer nanomedicine: A review of recent success in drug delivery. Clinical and Translational Medicine 2017; 6: 1–21. doi: 10.1186/s40169-017-0175-0.
13. Kumar S, Sharma R, Bhawna, *et al*. Prospects of biosensors based on functionalized and nanostructured solitary materials: Detection of viral infections and other risks. ACS Omega 2022; 7(26): 22073–22088. doi: 10.1021/acsomega.2c01033.
14. Kim HS, Hartgerink JD, Ghadiri MR. Oriented self-assembly of cyclic peptide nanotubes in lipid membranes. Journal of the American Chemical Society 1998; 120(18): 4417–4424. doi: 10.1021/ja9735315.
15. Webber MJ, Kessler JA, Stupp SI. Emerging pep-

tide nanomedicine to regenerate tissues and organs. Journal of Internal Medicine 2010; 267: 71–88. doi: 10.1111/j.1365-2796.2009.02184.x.
16. Yu C, Huang W, Li Z, *et al*. Progress in self-assembling peptide-based nanomaterials for biomedical applications. Current Topics in Medicinal Chemistry 2015; 16(3): 281–290. doi: 10.2174/1568026615666150701114527.
17. Song Q, Cheng Z, Kariuki M, *et al*. Molecular self-assembly and supramolecular chemistry of cyclic peptides. Chemical Reviews 2021; 121(22): 13936–13995. doi: 10.1021/acs.chemrev.0c01291.
18. Zhao X, Zhang S. Self-assembling nanopeptides become a new type of biomaterial. Advances in Polymer Science 2006; 203: 145–170. doi: 10.1007/12_088.
19. Rovero P, Quartara L, Fabbri G. Synthesis of cyclic peptides on solid support. Tetrahedron Letters 1991; 32(23): 2639–2642. doi: 10.1016/S0040-4039(00)78806-X.
20. Chow HY, Zhang Y, Matheson E, Li X. Ligation technologies for the synthesis of cyclic peptides. Chemical Reviews 2019; 119(17): 9971–10001. doi: 10.1021/acs.chemrev.8b00657.
21. Mandal D, Shirazi AN, Parang K. Cell-penetrating homochiral cyclic peptides as nuclear-targeting molecular transporters. Angewandte Chemie International Edition 2011; 50: 9633–9637. doi: 10.1002/anie.201102572.
22. Panigrahi B, Singh RK, Suryakant U, *et al*. Cyclic peptides nanospheres: A '2-in-1' self-assembled delivery system for targeting nucleus and cytoplasm. European Journal of Pharmaceutical Sciences 2022; 171: 106125. doi: 10.1016/j.ejps.2022.106125.
23. Kumar V, Van Rensburg W, Snoep JL, *et al*. Antimicrobial nano-assemblies of tryptocidine C, a tryptophan-rich cyclic decapeptide, from ethanolic solutions. Biochimie 2023; 204: 22–32. doi: 10.1016/j.biochi.2022.08.017.
24. Shimizu T, Ding W, Kameta N. Soft-matter nanotubes: A platform for diverse functions and applications. Chemical Reviews 2020; 120(4): 2347–2407. doi: 10.1021/acs.chemrev.9b00509.
25. Hamley IW. Peptide nanotubes. Angewandte Chemie International Edition 2014; 53(27): 6866–6881. doi: 10.1002/anie.201310006.
26. Priegue JM, Louzao I, Gallego I, *et al*. 1D alignment of proteins and other nanoparticles by using reversible covalent bonds on cyclic peptide nanotubes. Organic Chemistry Frontiers 2022; 9: 1226–1233. doi: 10.1039/d1qo01349a.
27. Katouzian I, Jafari SM. Protein nanotubes as state-of-the-art nanocarriers: Synthesis methods, simulation and applications. Journal of Controlled Release 2019; 303: 302–318. doi: 10.1016/j.jconrel.2019.04.026.
28. Ghadiri MR, Granja JR, Milligan RA, *et al*. Self-assembling organic nanotubes based on a cyclic peptide architecture. Nature 1993; 366: 324–327.
29. Garcia-Fandino R, Amorin M, Castedo L, Granja JR. Transmembrane ion transport by self-assembling α,γ-peptide nanotubes. Chemical Science 2012; 3: 3280–3285.
30. Yang NJ, Hinner MJ. Getting across the cell membrane: An overview for small molecules, peptides, and proteins. In: Site-specific protein labeling: Methods and protocols. Totowa: Humana Press; 2015. p. 29–53.
31. Surís-Valls R, Hogervorst TP, Schoenmakers SMC, *et al*. Inhibition of ice recrystallization by nanotube-forming cyclic peptides. Biomacromolecules 2022; 23: 520–529. doi: 10.1021/acs.biomac.1c01267.
32. Konda M, Bhowmik S, Mobin SM, *et al*. Modulating hydrogen bonded self-assembled patterns and morphological features by a change in side chain of third amino acid of synthetic γ- Amino acid based tripeptides. ChemistrySelect 2016; 1(11): 2586–2593. doi: 10.1002/slct.201600557.
33. Zhao K, Xing R, Yan X. Cyclic dipeptides: Biological activities and self-assembled materials. Journal of Peptide Science 2021; 113: e24202. doi: 10.1002/pep2.24202.
34. Tao K, Fan Z, Sun L, *et al*. Quantum confined peptide assemblies with tunable visible to near-infrared spectral range. Nature Communications 2018; 9: 3217. doi: 10.1038/s41467-018-05568-9.
35. Blunden BM, Chapman R, Danial M, *et al*. Drug conjugation to cyclic peptide-polymer self-assembling nanotubes. Chemistry–A European Journal 2014; 20(40): 12745–12749. doi: 10.1002/chem.201403130.
36. Mendive-Tapia L, Wang J, Vendrell M. Fluorescent cyclic peptides for cell imaging. Journal of Peptide Science 2021; 113: e24181. doi: 10.1002/pep2.24181.
37. Dougherty PG, Sahni A, Pei D. Understanding cell penetration of cyclic peptides. Chemical Reviews 2019; 119(17): 10241–10287. doi: 10.1021/acs.chemrev.9b00008.
38. Abriouel H, Lucas R, Omar NB, *et al*. Potential applications of the cyclic peptide enterocin AS–48 in the preservation of vegetable foods and beverages. Probiotics and Antimicrobial Proteins 2010; 2: 77–89. doi: 10.1007/s12602-009-9030-y.
39. Thorstholm L, Craik DJ. Discovery and applica-

tions of naturally occurring cyclic peptides. Drug Discovery Today: Technologies 2012; 9(1): e13–e21. doi: 10.1016/j.ddtec.2011.07.005.
40. Gran L. On the effect of a polypeptide isolated from "Kalata-Kalata" (Oldenlandia affinis DC) on the oestrogen dominated uterus. Acta Pharmacologica et Toxicologica 1973; 33(5): 400–408. doi: 10.1111/j.1600-0773.1973.tb01541.x.
41. Tam JP, Lu YA, Yang JL, Chiu KW. An unusual structural motif of antimicrobial peptides containing end-to-end macrocycle and cystine-knot disulfides. Proceedings of the National Academy of Sciences of the United States of America 1999; 96(16): 8913–8918. doi: 10.1073/pnas.96.16.8913.
42. Gerlach SL, Rathinakumar R, Chakravarty G, *et al*. Anticancer and chemosensitizing abilities of cycloviolacin O2 from *Viola odorata* and psyle cyclotides from *Psychotria leptothyrsa*. Biopolymers 2010; 94: 617–625. doi: 10.1002/bip.21435.
43. Pränting M, Lööv C, Burman R, *et al*. The cyclotide cycloviolacin O2 from *Viola odorata* has potent bactericidal activity against Gram-negative bacteria. Journal of Antimicrobial Chemotherapy 2010; 65: 1964–1971. doi: 10.1093/jac/dkq220.
44. Pinto MEF, Batista J, Koehbach J, *et al*. Ribifolin, an orbitide from jatropha ribifolia, and its potential antimalarial activity. Journal of Natural Products 2015; 78: 374–380. doi: 10.1021/np5007668.
45. Lázár V, Martins A, Spohn R, *et al*. Antibiotic-resistant bacteria show widespread collateral sensitivity to antimicrobial peptides. Nature Microbiology 2018; 3: 718–731. doi: 10.1038/s41564-018-0164-0.
46. Bechinger B, Gorr SU. Antimicrobial peptides: Mechanisms of action and resistance. Journal of Dental Research 2017; 96(3): 254–260. doi: 10.1177/0022034516679973.
47. Ribeiro R, Pinto E, Fernandes C, Sousa E. Marine cyclic peptides: Antimicrobial activity and synthetic strategies. Marine Drugs 2022; 20(6): 397. doi: 10.3390/md20060397.
48. Han H, Gao Y, Chai M, *et al*. Biofilm microenvironment activated supramolecular nanoparticles for enhanced photodynamic therapy of bacterial keratitis. Journal of Controlled Release 2020; 327: 676–687. doi: 10.1016/j.jconrel.2020.09.014.
49. Sulthana R, Archer AC. Bacteriocin nanoconjugates: Boon to medical and food industry. Journal of Applied Microbiology 2021; 131(3): 1056–1071. doi: 10.1111/jam.14982.
50. Shimomura Y, Ito M. Human hair keratin-associated proteins. Journal of Investigative Dermatology Symposium Proceedings 2005; 10(3): 230–233. doi: 10.1111/j.1087-0024.2005.10112.x.
51. Kung B, Anderson GH, Paré S, *et al*. Effect of milk protein intake and casein-to-whey ratio in breakfast meals on postprandial glucose, satiety ratings, and subsequent meal intake. Journal of Dairy Science 2018; 101(10): 8688–8701. doi: 10.3168/jds.2018-14419.
52. Winder SJ, Ayscough KR. Actin-binding proteins. Journal of Cell Science 2005; 118: 651–654. doi: 10.1242/jcs.01670.

Appendix

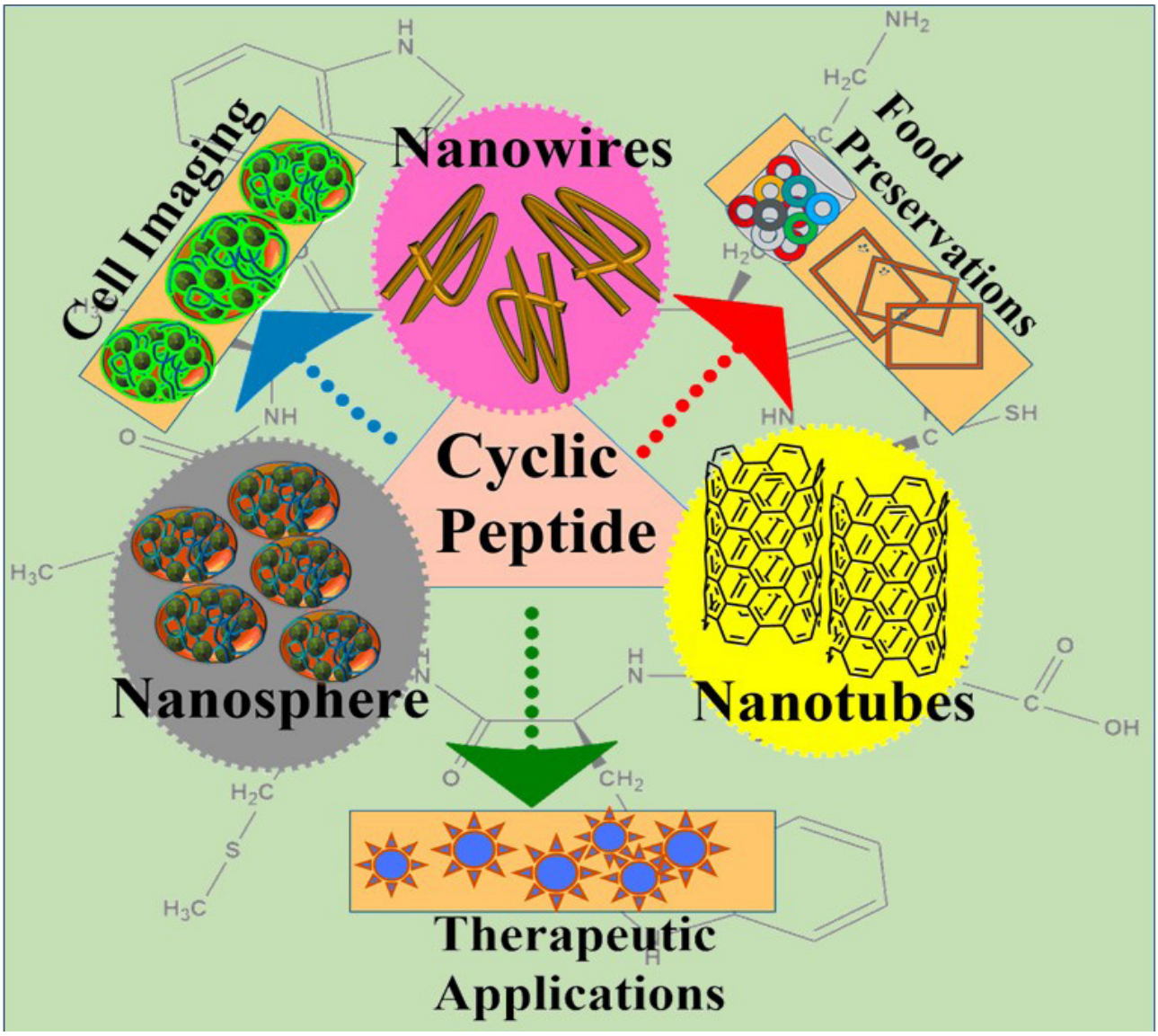


Figure A1. Graphical abstract.