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A Review: Peptide-Based Hydrogels Biomaterials: From Synthesis to Biomedical Applications

Nasmi Herlina Sari [a] *, Muhammad Zaidan Fadhlurrohman Rivlan [b], Senthil Muthu Kumar Thiagamani [c]

[a] Department of Mechanical Engineering, Faculty of Engineering, University of Mataram, Mataram, Indonesia
[b] Faculty of Medical, University of Mataram, Mataram, Indonesia.
[c] Department of Mechanical Engineering, Kalasalingam Academy of Research and Education, Srivilliputhur, India

Abstract. *Peptide-based hydrogel biomaterials (BHP) have emerged as novel therapeutic platforms for biomedical applications, providing accurate, efficient, and regulated drug delivery. This review examines the design, characterization, production, and biomedical applications of BHP, emphasizing their potential benefits in biomedicine. Advances in peptide synthesis techniques have permitted the creation of hydrogels with customized physicochemical properties to satisfy specific biomedical needs. Furthermore, this review delves into BHPs' biomedical uses, focusing on their role in improving therapeutic responses, allowing for sustained drug release, and reducing tumor growth. BHPs, with their biocompatibility, programmable hydrogel production, and adaptability, constitute a viable technique for addressing the problems of ovarian cancer treatment. This paper gives a thorough summary of current achievements in BHP research, bridging the gap between material development and clinical applications.*
Keywords: *hydrogel; biomaterial; peptide; cells; ovarian cancer.*

Type of the Paper: Article Review.

1. Introduction

Peptide-based hydrogels have received a lot of attention in the biomedical industry because of their biocompatibility, biodegradability, and ability to replicate the natural extracellular matrix [1–3]. Advances in peptide synthesis techniques have permitted the creation of hydrogels with adjustable physicochemical properties for a wide range of applications, including tissue engineering, drug delivery, and wound healing [4–12]. Several preliminary research results on BHP have reported on the development of molecular structure, physicochemical characterization, response to the environment, drug delivery, and pre-clinical and clinical trials [11–13]. Previous studies have been successful in creating peptide-based hydrogels with a range of complicated molecular architectures. Designing peptide sequences, arranging cross-links, and stimulating in situ polymerization are some of the steps involved in creating stable and controllable hydrogel networks [12,14,15]. The reaction of peptide hydrogels to modifications in the thermal, pH, and biological milieu—including the presence of specific biological molecules—has also been

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* First corresponding author
Email: nasmiherlina336@gmail.com

investigated in earlier research. In light of the evolving ovarian cancer landscape, this is crucial for improving drug delivery parameters and therapy response [6–8]. Peptide hydrogels have been investigated in a number of different studies for their potential to deliver growth hormones or chemotherapeutic medications to ovarian cancers, ovarian cancer therapy, and one key component of this research is controlled and precise drug delivery. The outcomes of pre-clinical and clinical trials using hydrogel biomaterials based on peptides for the treatment of ovarian cancer have also been published in a number of researches [6,7,16]. These findings provide insight on the security, efficiency, and tolerability of peptide hydrogels in humans; nevertheless, additional studies are required for validation and advancement. All things considered; these early study findings contribute to the establishment of a solid knowledge base for the creation of hydrogel biomaterials based on peptides in ovarian cancer therapy. These findings lay the groundwork for additional studies aimed at enhancing this technology's efficacy and clinical usability [17–19]. BHPs have several advantages over other biomaterials, such as biocompatibility, biodegradability, variable mechanical properties, or the ability to self-assemble under physical circumstances. Their molecular design enables precise control over structural and functional features, making them ideal for a wide range of biological applications, including drug delivery, tissue engineering, or wound healing. BHPs can imitate the extracellular matrix, facilitating cell adhesion, proliferation, and transformation more effectively over synthetic or non-peptide-based hydrogels. These characteristics contribute to their superior performance in biomedical applications. In the context of treating ovarian cancer, peptide-based hydrogel biomaterials (BHP) offer a number of significant benefits. It is possible to engineer peptides so that they selectively attach to surface molecules or receptors found on ovarian cancer cells. This lessens toxicity to nearby healthy tissue and enables the peptide hydrogel to precisely deliver therapeutic medicines to cancer-affected areas. Hydrogel biomaterials can serve as regulated medication delivery systems. Fig. 1 depicts the deployment of novel chemistries for hydrogel biomaterial production. Materials scientists, chemists, and biologists have used varied chemical and biological breakthroughs to create exquisitely changeable and stimuli-responsive hydrogel biomaterials.

It is possible to engineer peptides in hydrogel structures so that they release therapeutic drugs either gradually or in response to variations in the pH or enzyme concentration of the ovarian cancer environment. Moreover, medicinal medicines susceptible to deactivation or degradation can be shielded by BHP. A microenvironment formed by the hydrogel structure can shield the medication from proteolytic enzymes and unfavorable environmental factors [19,21,22]. Hydrogels can be designed to adapt to the specific shape of ovarian tumors, including their uneven surfaces and interstitial gaps. This enables the hydrogel to potentially enhance drug penetration into the tumor by reaching dormant cancer cells. Peptide hydrogels can lessen the negative effects

of traditional medicines like systemic chemotherapy by selectively directing therapeutic chemicals to ovarian cancer cells. Both the patient's quality of life and the therapy's tolerability may benefit from this. BHP have the potential to be a novel therapeutic platform for the treatment of ovarian cancer due to their combination of these benefits. Peptide hydrogel therapy for ovarian cancer has the potential to improve treatment outcomes, lessen adverse effects, and lengthen the survival of patients [20,21,23].

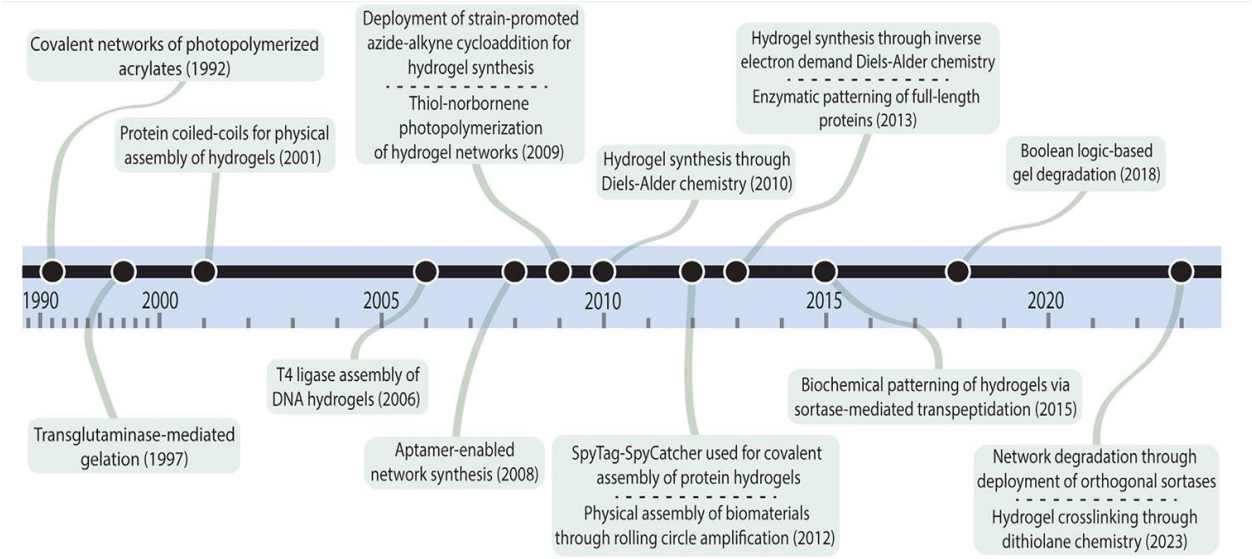

Fig. 1. Key milestones in the deployment of new chemistries for hydrogel biomaterial synthesis 1990-2020 [20]

A number of crucial steps are involved in the creation of peptide-based hydrogels biomaterial, including peptide design, synthesis, hydrogel formation, physicochemical characterization, optimization and modification, and preclinical and clinical testing. Creating the right peptide sequences to generate the ideal hydrogel structure is the first step in the development process. Peptides can be engineered to possess diverse physicochemical characteristics, like binding potency, solubility, and environmental responsiveness, in order to accomplish particular objectives in medicinal uses. Next, using the proper chemical or biological methods, the intended peptide is produced. Solid peptide synthesis, recombinant expression techniques in genetically modified organisms, and multistep chemical synthesis are examples of synthesis processes. After that, a three-dimensional network construction technique is used to shape the produced peptides into a hydrogel structure [22,24,25]. Numerous techniques, such as in situ polymerization, agglomeration, and cross-linking, can be used to accomplish this. In addition, the hydrogel's physicochemical characteristics were examined to comprehend its characteristics. The examination of morphology, pore structure, mechanical strength, elasticity, permeability, and reaction to the environmental factors, both biological and physical, is involved. To enhance its functionality and suitability, the hydrogel can be adjusted or changed in light of the

characterization findings. To increase the hydrogel's functionality, this could involve adding active ingredients, arranging cross-links, altering the hydrogel's surface, or combining it with other materials. BHP ought to undergo preclinical and clinical testing following their initial creation in order to assess their efficacy, toxicity, and tolerability for ovarian cancer therapy [20,21,23]. In order to advance the creation of more inventive and successful ovarian cancer therapies, scientists and professionals in a variety of domains, including chemistry, biology, materials science, and medicine, must collaborate in the development of BHP. Despite its advantages, BHP still faces numerous issues that must be addressed. One key concern is their mechanical stability, which may be inappropriate for load-bearing applications. Furthermore, achieving predictable and reliable degradation rates remains difficult, as BHP breakdown can vary according to environmental conditions. Scalable and cost-effective synthesis are also major challenges, restricting large-scale manufacturing and commercialization. Furthermore, a better understanding of their long-term bio compatibility and potential immune responses is required for clinical application.

Therefore, this review provides a comprehensive analysis of recent advancements in peptide-based hydrogels (BHP), concentrating on their synthesis, characterization, and use in the biomedical field, with a particular emphasis on tissue engineering, drug administration, wound healing, and existing constraints. Unlike prior evaluations, we focus the most recent advances in molecular engineering techniques to improve BHP performance and address existing issues. This study is an invaluable resource for researchers and industry people working to promote the development and implementation of BHP in biomedical disciplines.

2. Peptide-Based Hydrogels Biomaterials (BHP)

Peptide-based hydrogel biomaterials (BHP) are three-dimensional networks generated by the self-assembly of peptides. BHPs have been demonstrated to exhibit unique properties like as biocompatibility, biodegradability, and high water-uptake, which make them attractive candidates for a variety of medicinal applications, including ovarian cancer therapy. Typically, they require designing peptides capable of self-assembly via non-covalent interactions like hydrogen bonding, hydrophobic interactions, and π-π stacking. The design in Fig. 2 depicts the self-assembly of peptide-based hydrogels, emphasizing their production and biomedical uses. Monomers interact by molecular forces, resulting in secondary structures including β-sheets, α-helices, and random coils. These structural motifs initiate the self-assembly process, which results in the production of higher-order nanostructures such as vesicles, tubes, and fibrils. These nanostructures improve the mechanical and functional properties of the hydrogel, making it suitable for use in a variety of biomedical applications including drug administration, biological imaging biosensors, wound healing, three-dimensional in shape cell culture, or tissue engineering [26].

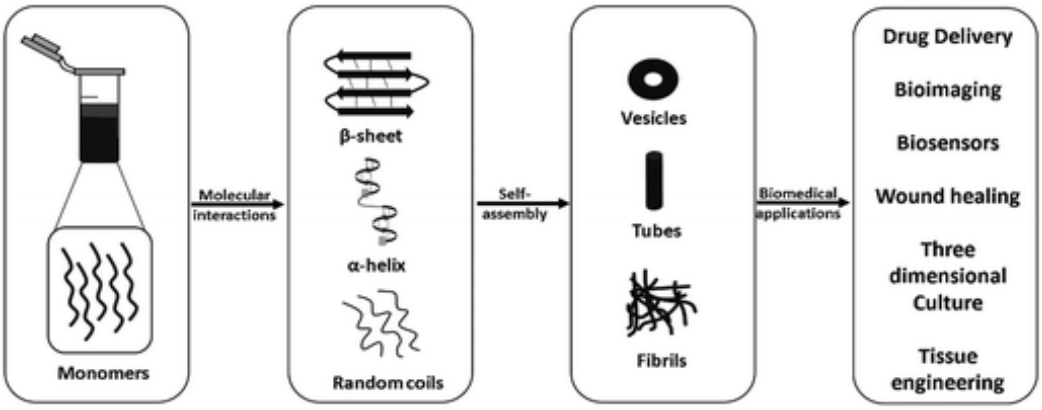

Fig. 2. Schematic of the self-assembly of peptides into different nanostructures and their possible applications [26].

Recent advances in the synthesis and application of peptide hydrogels demonstrate significant promise in enhancing therapy techniques for ovarian cancer, enabling for targeted delivery of therapeutic medicines to tumors [27–30]. However, a number of obstacles remain to be addressed through more study, including design complexity, bio compatibility and toxicities, drug delivery constraints, biodegradability [24,25], or manufacturing.

3. Properties of BHP

3.1. Biocompatibility

Because of their special blend of chemical, biological, and physical characteristics, hydrogels based on peptides are an attractive and promising class of biomaterial for use in biomedical applications. Since most peptides utilized in biomaterials are naturally occurring proteins found in the human body, they frequently show excellent biocompatibility with biological tissues, which is shown in detail in Fig. 3 [31]. This reduces the likelihood of immunological responses or the body rejecting the biomaterial once it is inserted [24,31].

Alpha helices, beta sheets, and intricate three-dimensional folds are examples of the orderly, repetitive structures that peptides can naturally generate. This process enables the production of biomaterials with distinct shapes and characteristics that can be tailored to meet specific application needs [32–34].

3.2. Morphology

BHPs vary in morphology according on their chemical composition as well as structure. Gel structures, which are three-dimensional networks made up of water, are prevalent in BHPs [35]. Hydrogels are a frequent form of BHP utilized in biomedical applications since they contain enough density and elasticity to be considered gels. These hydrogels are distinguished by a gelatin-like or tooth gel-like texture, as well as equally spaced holes. The size of these pores varies based

on the material composition and manufacturing procedure. These hydrogels have a network or fiber structure that is tightly or loosely linked. Biological cells can adhere to these structures and grow to build a three-dimensional network [36,37].

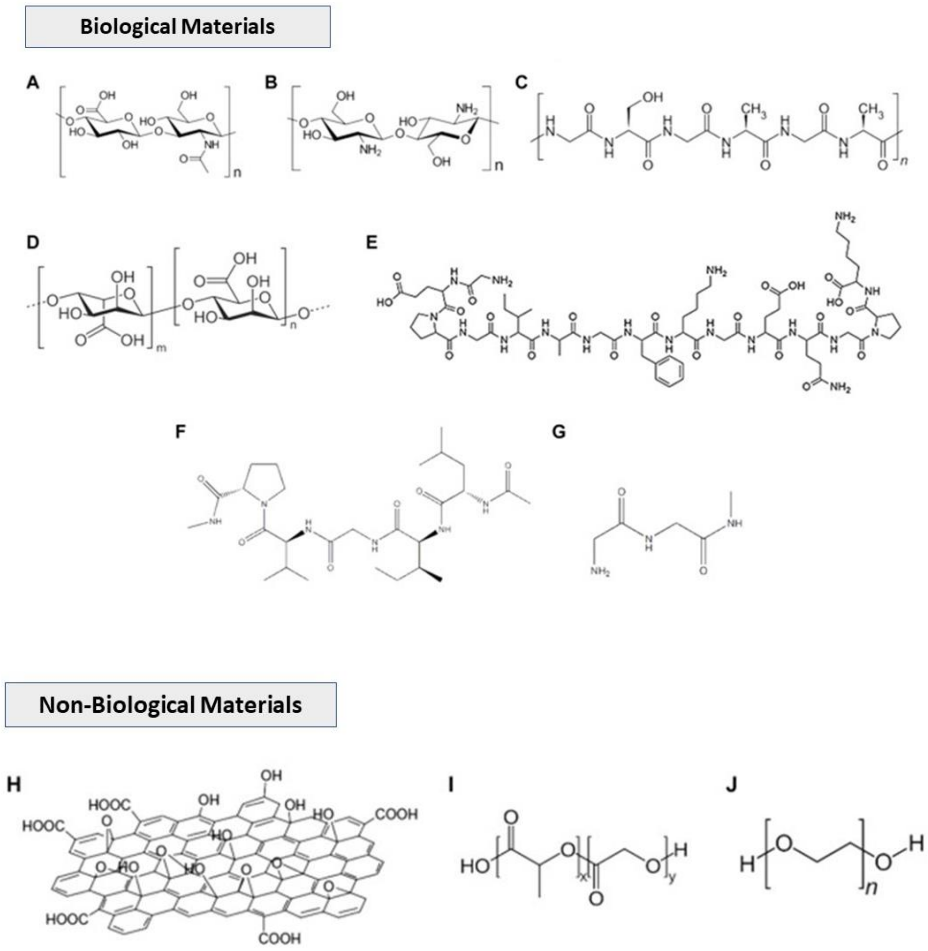

Fig. 3. Schematic of selected biological and non-biological materials used for tissue regeneration: (A) alginate; (B) chitosan; (C) silk; (D) hyaluronic acid; (E) type II-collagen; (F) elastin; (G) fibrin; (H) graphene oxide; (I) poly(Lactide-co-Glycolide) (J) poly(ethylene glycol) [32]

BHP's unusual morphological properties make it valuable in a variety of biological applications, including drug administration, medical imaging, and tissue creation. During the manufacturing process, BHP can exhibit a variety of morphological forms, such as reticular networks, fibrous structures, and porous architectures. These structural differences have a substantial effect on the hydrogel's permeability, water holding capacity, and response to external stimuli. Advanced imaging techniques like light and microscopy with electrons can be utilized to examine the morphological properties of hydrogels [38]. As demonstrated in Figs. 4a and 4b, the hydrogel microstructure is mostly made up of a thick and linked microfibre network. This arrangement corresponds to a generally homogenous fiber distribution with tiny fiber diameters. Fig. 4b demonstrates that sample EDP-2 (Fmoc-FFAAAKAA-NH_2) has a larger fiber density than

EDP-1 (Fmoc-FFAAAAKAA-NH_2), as shown in Fig. 4a, which could be attributable to differences in the synthesis technique or sample treatments. This well-organized nanofiber structure is frequently associated with superior thermal and mechanical properties, making it ideal for applications requiring robust and stable biomaterial composites. In contrast, EDP-3 (Fmoc-FFAAAKAAA-NH_2) exhibits a significant morphological difference from the previously described structure. Conversely, EDP-3 (Fmoc-FFAAAKAAA-NH_2) has a significant morphological difference from the previously observed structure. The fiber network seems fragmented, with fewer and more widely spread fibers (Fig. 4c). Furthermore, certain fibers exhibited aggregation or clustering, that might be attributed to changes in processing conditions, chemical alterations, or fiber-fiber interactions that influence dispersion and agglomeration. These morphological alterations are known to have a direct effect on the final hydrogel's physical and mechanical properties, particularly its tensile strength and thermal stability. Further research is required to completely understand the underlying mechanisms producing these structural variances and their consequences for hydrogel performance in biomedical and industrial applications. The EDP-2 peptide was discovered to make not only structurally coherent hydrogels, but also nanofibers of higher quality than EDP-1 and EDP-3. The EDP-2 peptide resulted in the longest and densest nanofibers, reaching at least 4.57 µm (Fig. 4b), while EDP-1 produced intermediate fibers measuring at least 1.86 µm. The EDP-3 peptide produced the smallest fibers, measuring 0.649 µm (Fig. 4c) [39].

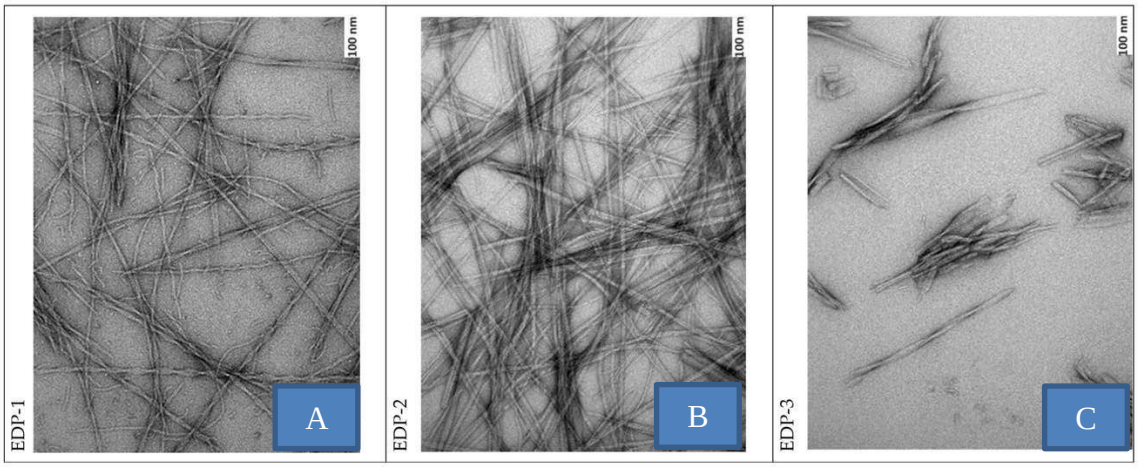

Fig. 4. TEM morphology of the three peptides (scale bar= 100 nm), a. EDP-1, b. EDP-2, and c. EDP-3 [39].

3.3. Mechanical Strength

The mechanical properties of BHP are critical in their applicability for ovarian cancer therapy, particularly their strength, elasticity, and resistance to deformation. These qualities determine the hydrogel's capacity to preserve its rigidity when used as a drug delivery matrix or scaffold in tissue engineering. The mechanisms governing these mechanical qualities are tightly linked to the hydrogel's internal structure. Hydrogels are composed of a three-dimensional polymer

network that is capable of absorbing significant volumes of water. This structure is created by a cross-linking reaction between polymer chains, that can occur physically or chemically, as seen in Fig. 5. Fig. 5 depicts the interactions between materials and peptides over the production process, emphasizing five main interaction types. At first, peptides or biomolecules are delivered to the material surface, and they interact via multiple mechanisms: (1) Peptides cling to the surface by weak van der Waals forces or hydrophobic interactions rather than chemical bonds, resulting in a reversible attachment. (2) Covalent bonding occurs among functional chains on the peptide and the material's surface, resulting in a stable and irreversible link. (3) Peptides are bound to the material through electrostatic, hydrogen bonding, and π-π stacking interactions, which provide moderate stability. (4) Peptides become physically trapped inside the material's structure, generally within holes or networks, assuring retention in the absence of strong chemical bonds, and (5) The material undergoes surface modification, enabling stronger and more specific binding interactions with peptides, enhancing stability and functionality. In contrast, peptides can be incorporated into biomaterials through simple absorption, covalent conjugation, molecular reactions, entrapment, or chemically modified [31]. The density and kind of cross-linking affect the hydrogel's strength and flexibility. Furthermore, the quantity of cross-linking in the hydrogel, carrier concentration, and peptide composition have all been shown to influence BHP mechanical strength [39–41].

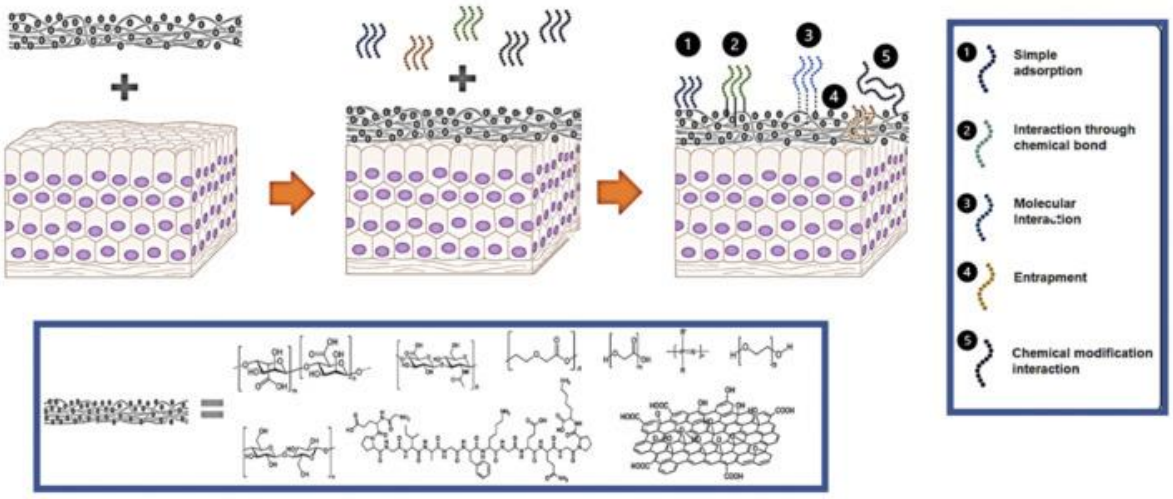

Fig. 5. Illustration of material-peptide interactions and the manufacturing process [32].

BHP's mechanical strength can be increased through a variety of means, including the use of crosslinkers or the combination with other materials. Adding β-TCP and PEG to PVA hydrogels increased mechanical parameters such as compressive strength or elastic modulus, making them suitable for injectable biomaterials. In addition, BHP's elasticity enables it to adapt to dynamic biological contexts [41]. According to Indriyani et al. [42], the physical structure and elasticity

caused by crosslinking in the hydrogel system allow this material to stretch or contract in response to environmental factors such as temperature, pressure, or pH.

3.4. Density and Porosity

The density and porosity of hydrogels affect their capacity to take up water, offer an environment conducive to cell growth, and make it easier for nutrients and metabolites to be exchanged. High porosity hydrogels have a propensity to absorb large amounts of water and can efficiently promote cell proliferation [43].

3.5. Texture

The density, viscosity, and physical structure of a hydrogel are correlated with its texture and consistency. Denser, stiffer hydrogels can be found alongside liquid forms that resemble gels [44]. The ease of manipulation, application, and usage of hydrogels in diverse biomedical contexts may be influenced by this texture [45]. Designing, refining, and utilizing hydrogels for particular uses in tissue engineering, drug delivery, and other therapies requires a thorough grasp of the physical characteristics of BHP. Researchers can create hydrogels that are tailored to the particular requirements of their applications by taking these physical characteristics into account.

3.6. Chemical Properties

Peptide composition, carrier material, and synthesis circumstances can all affect the chemical characteristics of hydrogels containing BHP [13,46–48]. Peptides and carrier materials' chemical characteristics can affect hydrogels' solubility in different solvents. Depending on how the peptide molecules interact with the carrier material, hydrogels can dissolve in water, some organic solvents, or inorganic solvents. Particularly if the peptides have been altered to include more functional groups, BHP may display some degree of chemical reactivity. This can involve processes like the conjugation of medications or bioactive compounds with one another, or the creation of covalent bonds by crosslinking events. Hydrogel peptides typically contain amine, carboxylic, hydroxyl, or sulfhydryl groups, among other functional groups, as shown in Table 1 [48–51].

The hydrogel's ability to interact with ions, other molecules, or proteins, among other things, can be affected by the presence of these functional groups. Certain ionic behavior can be seen in the hydrogel if the peptides have charged functional groups, such as amine or carboxylic acid groups [54–56]. The ability to absorb or release ions from solution, the capacity for ion exchange, and the reaction to variations in pH or ion concentration are a few examples of these. BHP often have a high absorption rate for water in their matrix. This is because the hydrophilic groups included in the peptides and carrier materials produce a moist and favorable environment for cell growth or the delivery of drugs that dissolve in water within the hydrogel [52,54,55,57]. Reversible characteristics refer to the ability of certain BHP to alter their structure in response to variations in

external factors like pH, temperature, or ion concentration [46,58,59]. This makes it possible to precisely manipulate the hydrogel's characteristics and create more versatile uses. In order to effectively use hydrogels in a range of biomedical applications, such as drug delivery, tissue engineering, and other medical therapies, their chemical properties are crucial.

Table 1. The chemical properties of different types of amino acids [52,53]

No.	Amino Acids	Properties
(1)	Aliphatic hydrophobic I. Alanine (Ala, A) II. Leucine (Leu, L) III. Isoleucine ((Ile, I) IV. Valine (Val, V) V. Methionine (Met, M)	Imparts a general hydrophobic environment
(2)	Aromatic hydrophobic I. Phenylalanine (phe, F) II. Tyrosine (Tyr, Y) III. Tryptophan (Trp, W)	Involved in π- π stacjing, which is important for protein and peptide folding.
(3)	Hydrophylic, uncharged I. Asparagine (Asn, N) II. Gutamine (Gln, Q) III. Serine (Ser, S) IV. Threonine (Thr, T)	The -OH or -CONH groups are involved in hydrogen bonding interactions
(4)	Positively charged (Basic) I. Histidine (His, H) II. Arginine (Arg, R) III. Lysine (Lys, K)	Involved in specific charge-charge interactions, by either exploiting attraction between oppositely charged groups or using repulsive forces between two equal charges.
(5)	Negatively charged (Acidic) I. Glutamic acid (Glu, E) II. Aspartic acid (Asp, D)	Involved in specific charge-charge interactions, , by either exploiting attraction between oppositely charged groups or using repulsive forces between two equal charges.
(6)	Specialized I. Cysteine (Cys, C) II. Glycine (Gly, G) III. Proline (Pro, P)	I. A target for chemical modification, either inter-peptide or between and other structures. II. Responsible for a high degree of flexibility, by removing steric hindrances. II. Responsible for a high degree of rigidity due to locked conformation.

3.7. Water storage

Significant water retention in the matrix is a known property of hydrogels based on peptides. Due of this, it can be used for things like delivering water-soluble medications or creating a moist environment for cell growth [44,60]. The chemical makeup and physical structure of peptide-based biomaterial hydrogels play a major role in their capacity to hold big volumes of water within their matrix. Hydrophilic functional groups like amine, carboxylate, or hydroxyl groups are more common in hydrogel peptides [61–63]. Encouraging the hydrogel to draw and hold water inside its matrix, these groups exhibit a strong attraction for water. Peptide-based biomaterial hydrogels can be structured to include holes or empty spaces that are capable of efficiently retaining water

[61–64]. The hydrogel's ability to absorb water is enhanced by these pores, which offer more surface area for water-hydrogel interaction. Water molecules can become trapped in the hydrogel matrix when functional groups on peptides establish hydrogen bonds with them. These hydrogen bonds can also give the hydrogel structural stability and guard against abrupt changes in the hydrogel's volume when it absorbs or releases water [61,65,66]. A small percentage of hydrogels based on peptides exhibit swelling behavior, meaning they can absorb a lot of water and grow substantially in volume [67,68].

The reason behind the hydrogel's ability to hold onto water in its matrix is the equilibrium between the hydrophilic force of attraction of water and the hydrophobic compressive force of the hydrogel structure [24,69,70]. A hydrogel's ability to retain water in addition to peptides can be affected by the composition of its carrier material. Carriers with hydrophilic properties or high capacities for water absorption can enhance hydrogels' ability to retain water in their matrix [70,71].

BHP have a considerable capacity to hold a lot of water in their matrix by utilizing a mixture of these methods. This characteristic is critical for applications like tissue engineering, drug delivery, and establishing a moist environment for cell growth. Properties, in which alterations in the hydrogel's structure can be reversed in reaction to shifts in outside factors like pH, temperature, or ion concentration [72,73]. More flexible uses are made possible by this exact control of the hydrogel's characteristics [74–77].

Hydrogel performance and applicability in many biomedical applications, such as drug delivery, tissue engineering, and other medical therapies, are largely dependent on the chemical characteristics of these peptide-based biomaterial hydrogels [74,75,78,79].

4. Applications

4.1. Drug Delivery

Biomaterials based on peptides are frequently employed as precise and regulated drug delivery systems for a range of medical conditions, such as tissue regeneration, inflammatory illnesses, and cancer therapy [6–8]. Peptide-based hydrogels replicate the physical and chemical properties of ECM, making them suitable for a wide range of therapeutic applications, including neuroinflammation reduction, neural tissue regeneration promotion, and immunomodulation support. These hydrogels can function as cell carriers, medication delivery vehicles, and bridges to connect injured tissues (Fig. 6a). BHP promote neuron regeneration by generating an environment high in growth factors like NGF, BDNF, and GDNF. These hydrogels can activate endogenous NSCs and promote neuronal cell differentiation to aid in the recovery of central nervous system tissues (Fig. 6b). These hydrogels can help with drug delivery to specific locations in the central nervous system (CNS) by bridging the blood-brain barrier (BBB). These applications

include the regulated release of medicines like Taxol to promote nerve regeneration and functional recovery following CNS injury (Fig. 6c) [80] .

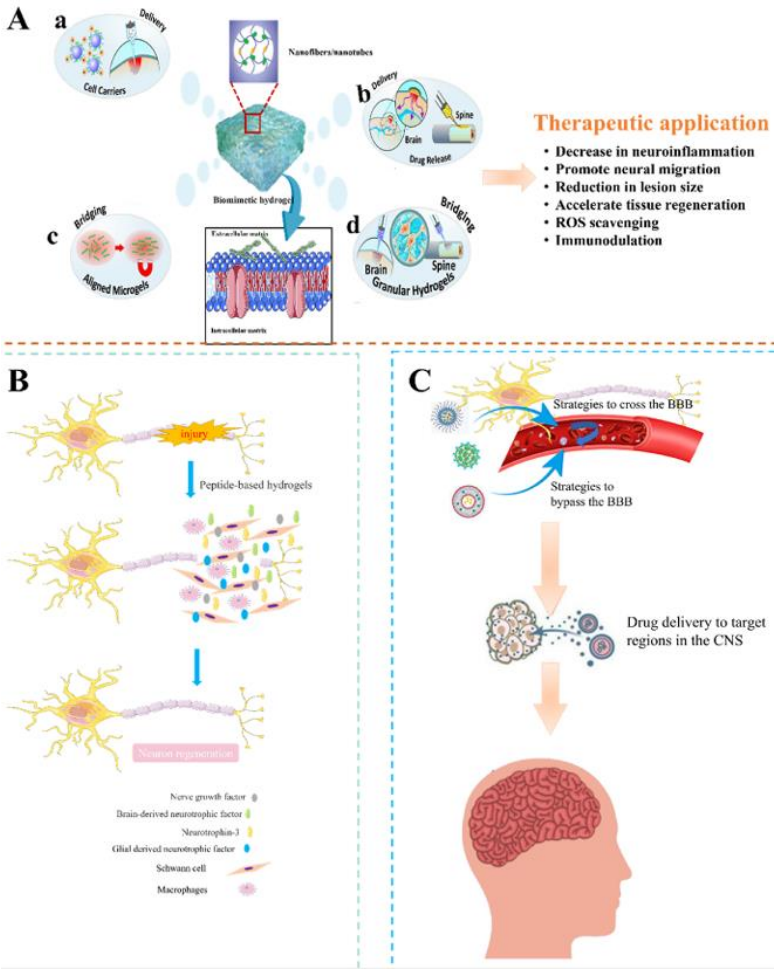

Fig. 6. (a) Peptide-based hydrogels in diverse applications associated with neural regeneration and therapy. (b) By transplanting exogenous neural stem cells through peptide-based hydrogels, the secretion of various growth factors and neurotrophic proteins can be promoted near damaged tissues, creating a favorable environment for nerve regeneration, and (c) Graphical overview of the process toward of peptide-mediated treatment of neurological diseases [80]

4.2. Tissue Engineering

BHPs have emerged as important components in tissue engineering, providing a foundation that resembles the natural extracellular matrix. Their ability to construct three-dimensional structures that promote cell development and differentiation makes them excellent candidates for these applications. In tissue engineering, peptide-based hydrogels can be utilized to promote cell proliferation and differentiation, create an extracellular matrix resembling the natural environment, and aid in tissue regeneration [12,81].

4.3. Wound Care

Peptide-based hydrogels have gained popularity in wound care due to their ability to imitate the natural extracellular matrix, thereby offering a supportive environment for tissue regeneration.

These hydrogels are useful for wound dressings because of their biocompatibility, biodegradability, and ability to adjust physical and chemical properties. According to Nizam et al. [82], BHP have considerable potential in chronic wound healing since they stimulate tissue regeneration and offer adjustable properties. They can be used to wounds to promote tissue regeneration and healing, reduce infection risk, and increase patient comfort [80]. Liu et al. [83] discovered that peptide-based hydrogels can create structures that promote cell development in tissue engineering applications. Furthermore, peptide-based hydrogels can be programmed to respond to specific stimuli, such as pH changes or the presence of specific enzymes, enabling the controlled release of medicines or growth factors at the wound site.

4.4. Implants and Injury Recovery

BHP has showed considerable promise in implant applications and injury rehabilitation due to its ability to replicate the natural extracellular matrix and facilitate tissue regeneration. This hydrogel's biocompatibility, biodegradable properties, and ability to alter mechanical pressures make it a suitable matrix for supporting the healing and restoration of damaged tissues BHP [12,83]. Mukherjee et al. [84] discovered that traumatic brain damage and spinal cord injury cause millions of fatalities and physical disabilities each year, and that peptide-based hydrogels provide a viable therapeutic method for mending central nervous system injuries. Liu et al. [83] created an injectable peptide-based hydrogel implant that can easily fill uneven shapes and form a self-sustaining solid at the injured region, with significant promise in biomedical applications.

4.5. Muscle Recovery and Bone Damage

Because of its capacity to replicate the natural extracellular matrix and promote tissue regeneration, BHP has demonstrated considerable promise in muscle recovery and bone injury repair applications [12]. This hydrogel's biocompatibility, biodegradability, and ability to alter mechanical pressures make it excellent as a matrix for wound healing and tissue restoration. Hao et al. [85] found that bioactive peptides and proteins can modify the tissue microenvironment, which is critical for tissue repair and regeneration.

5. Synthesis of PBH

5.1. Mixing Peptide Solution with Carrier

In this procedure, a peptide solution and a carrier material solution—such as a natural or synthetic polymer—that can create a hydrogel are mixed together. Peptide solutions are often made in appropriate solvents; however, carrier solutions can also be made with water or certain organic solvents. Following mixing, a variety of activities, including hydrophobic interactions, the creation of hydrogen bonds, and chemical or physical crosslinking, lead to gelation [85,86].

5.2. Hydrogel Formation through Chemical Reactions

This approach forms a hydrogel by use of specific chemical interactions between peptides

and carrier molecules. Chemical processes that are commonly employed include those that crosslink functional groups on peptides and carrier materials, like those that occur between amine and carboxylic acid groups.

5.3. Peptide Self-Assembly Process

A mechanism known as self-assembly enables some peptides to organize into hydrogel structures on their own. Peptides are engineered with particular amino acid sequences in this technique to enable non-covalent interactions between peptide molecules, like the creation of interacting beta sheets or helical shapes [86,87].

Researchers built a dipeptide gel using self-assembly in varied solvents and salt concentrations, as shown in Fig. 7a. In vitro investigations demonstrated that glial cells (C6) can grow on the biocompatible and robust dipeptide hydrogel. Furthermore, as shown in Fig. 7a, the cytoskeletal composition increased proportionally with increasing sodium acetate concentration, demonstrating a favorable correlation between sodium acetate concentration and glial cell development. Adak et al. [88] created an injectable and biocompatible peptide hydrogel with sulfonyl activity. The hydrogel was made from the *Phe-Phe* dipeptide and included a peptide sequence with a sulfate functional group at the N-terminus that was produced using para-mercaptobenzoic acid. A PLGL tetrapeptide linker was used to connect the neuroprotective hexapeptide (NV) at the C-terminus, as shown in Fig. 7b.

These findings highlight the significant potential of biocompatible and robust dipeptide hydrogels as adaptable platforms for promoting glial cell proliferation and creating an ideal milieu for brain tissue regeneration.

5.4. Hydrogel Formation via Water-Free Drying

One way to create peptide-based hydrogels without the need for gelation or chemical crosslinking is by water-free drying and hydrogel creation. In order to create a three-dimensional thick network that resembles a hydrogel, this procedure involves removing water from the peptide solution and carrier substance. A peptide-based gel structure is created using this method by gradually drying the peptide solution and carrier material. With the removal of water from the solution, a stable three-dimensional network is formed, facilitating the creation of a hydrogel structure.

The general procedures for creating hydrogels through water-free drying are as follows: First, preparation of Peptide Solution and Vehicle: One way to make peptide solutions is to dissolve them in appropriate solvents, including water or certain organic solvents. The carrier material is also made into a solution with the proper composition and concentration. Second, the process of mixing the peptide solution and carrier solution involves ensuring that the proper proportions are followed. To guarantee an even distribution of the peptides within the hydrogel

that is created, this combination needs to be homogenous and even. Third, diluting the mixed solution: Next, the peptide solution and carrier material combination is spread out on a spotless, level surface, like a Petri dish glass or plate. Depending on the needs of the application, the mixture can be dried by keeping it out in the open at normal temperature or at a controlled temperature. A solid structure made of peptides and carrier materials—the hydrogel—is left behind as the water in the solution gradually evaporates during drying. The hydrogel that has been created is deposited from the drying site's surface following the completion of the drying process [88,89]. Depending on the size and shape of the drying container, hydrogels can take on a variety of forms and dimensions. The mixture is dried by being left out in the open at room temperature or, depending on the needs of the application, at a certain temperature. The hydrogel is composed of a solid structure of peptides and carrier molecules that is formed as the water in the solution gradually evaporates during drying [88,89]. Fourth, dry solution deposition: The generated hydrogel is deposited from the drying site's surface following the completion of the drying process. Depending on the size and shape of the drying container, hydrogels can take on a variety of shapes and sizes.

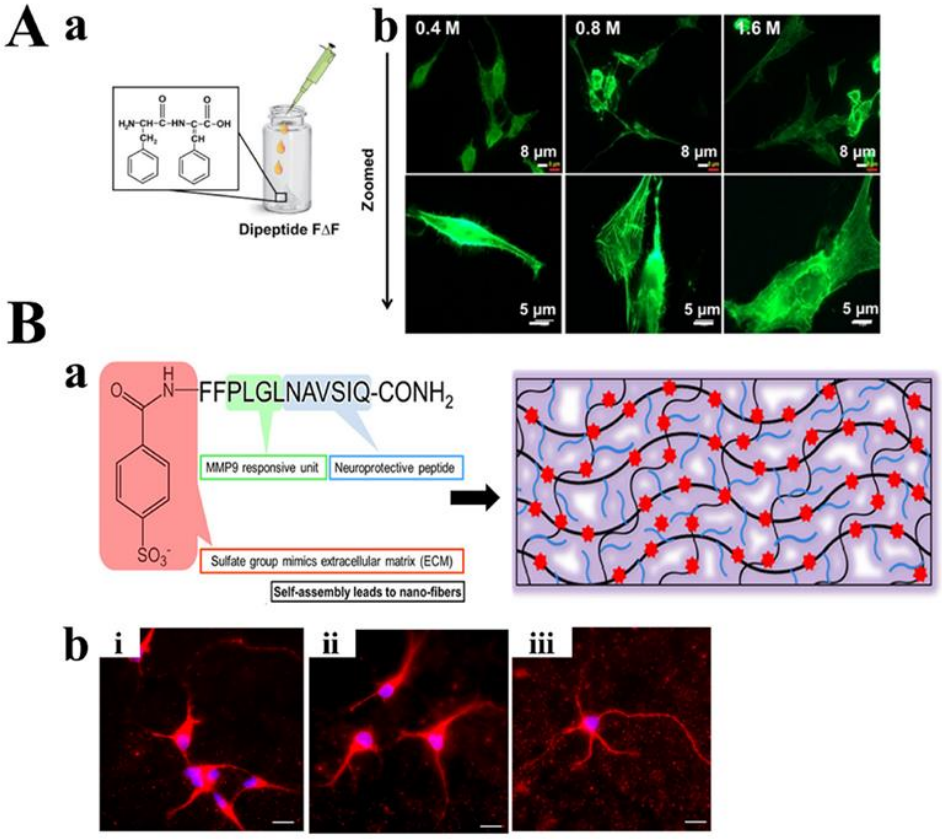

Fig. 7. Dipeptide hydrogels are used for nerve regeneration, (A) Fluorescence microscopy images of C6 glial cells cultivated on *Phe-Phe* hydrogels produced with different amounts of sodium acetate. (B) Cortical neurons from a rat brain were cultured in the presence of SFNV hydrogel (a) at day 1, and (b) at day 3, (c) at day 7 [88].

6. Conclusions

Lately, there has been a notable advancement in the creation of hydrogel biomaterials based on peptides. With the quick advancement of hydrogel synthesis, characterization, and manufacturing, more complex, controlled, and high-performing materials may now be produced. An inventive and practical way to address treatment-related obstacles is through the use of peptide-based hydrogels in ovarian cancer therapy. BHP provide significant potential to enhance the prognosis of patients suffering from ovarian cancer due to their capacity to target tumors with medications, decrease toxicity to healthy tissue, and boost therapeutic efficacy. The creation of BHP for ovarian cancer treatment still faces a number of obstacles in spite of considerable advancements. Enhancing hydrogel stability in the body's intricate and dynamic milieu is one of the primary problems. Furthermore, more research is required to enhance drug delivery efficiency, control drug release, and hydrogel penetration into tumors. To expedite the transition of these innovations from the laboratory to pertinent clinical applications, interdisciplinary collaboration is also essential. We can extend the survival and enhance the quality of life for ovarian cancer patients by further developing and refining BHP. This will also open the door for the future creation of more sophisticated and individualized cancer treatments. To address these problems, further research and interdisciplinary collaboration are required to fine-tune hydrogel formulations, increase biocompatibility, and hasten clinical translation. Moving forward, a collaborative effort among materials scientists, oncologists, or biomedical engineers is required to realize the full potential of PBHs in cancer. By furthering these advances, we can not only increase ovarian cancer patients' survival rates and quality of life, but also set the framework for the development of the next-generation, individualized cancer medicines.

CRediT authorship contribution statement

Nasmi Herlina Sari: Conceptualization, Methodology, Writing – original draft, Writing-review & editing, Supervision. **Muhammad Zaidan Fadhlurrohman Rivlan**: Resources, Data curation, Visualization. **Senthil Muthu Kumar Thiagamani**: Resources, Data curation, Visualization.

Declaration of Competing Interest

The authors declare no conflicts of interest

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