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Understanding the multifaceted nature of peptide hydrogels in biomedical research

Srestha Ghosh[1,†], Shinjini Chaudhuri[1,†], Subhabrata Guha[1], Gaurav Das[1,*]

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Abstract

Hydrogels are networks of three-dimensional cross-linked polymers, which possess the capacity to absorb and retain water. Hydrogels have proven to be adaptable and versatile, making them useful in various biomedical applications such as tissue engineering and regenerative medicine. Among the various types of hydrogels, peptide-based hydrogels are most suited for biological applications due to their special features, which include biodegradability, mechanical stability, biocompatibility, capacity to retain more water, injectability, and elasticity like that of tissues. In this review, we will present the recent advancements that have occurred in the field of peptide-based hydrogels concerning its biomedical applications especially delivery of targeted delivery, wound healing, tissue engineering, stem cell therapy, etc.

Keywords: *hydrogel, peptide, biocompatible, tissue engineering, anti-cancer drug*

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1. Introduction

Self-assembly in supramolecular chemistry permits the synthesis of nanoscale materials, giving rise to attributes like toughness and fibrous network architecture. Hydrogels are the most common nanomaterials with potential uses for biomedical purposes [1]. Multiple definitions of hydrogels have been explored by researchers over the years. A hydrogel is a three-dimensional (3D) arrangement of hydrophilic, cross-linked water-swollen polymers that is capable of imbibing, swelling, and withholding water without modifying its architecture [2]. The cross-links between monomers enable them to resist dissolution [3]. The functional groups connected to the polymers such as carboxylate, sulfate, amine, and hydroxyl groups are hydrophilic in nature and provide hydrogels with their capacity to absorb water [4]. Hydrogels are grouped into natural, semi-synthetic, and synthetic based on their origin [5]. The polymeric composition of a hydrogel can also be used to classify it. While copolymeric hydrogels are made up of many monomer species with at least one hydrophilic component, homo-polymeric hydrogels are polymer networks produced from individual monomer species. An important family of hydrogels called the multipolymer interpenetrating polymeric hydrogel is composed of two different cross-linked polymer components that are held together in a network [6]. Based on their chemical configuration, hydrogels can be grouped as amorphous, semi-crystalline, and crystalline, respectively [7]. The technique of cross-linking primarily divides hydrogel into two general groups. Rigid and inflexible covalent bonds that join the network together constitute chemical hydrogel. These stubborn interactions result in irreversible hydrogels that experience considerable volume changes when they move from the solution state to the gel state [8]. In contrast, secondary molecular interactions like hydrogen bonds, electrostatic interactions, and $\pi-\pi$ interactions hold the networks in physical gels together. Alterations in the surrounding environment, including temperature, pH, and stress, can easily hamper these interactions. As a result, the synthesis of physical gel is revertible and gel formation is rapid [9]. The versatility and multifunctionality of peptide hydrogels allow them to serve as a promising material for numerous biomedical applications [10]. Internal and external trigger factors such as pH, metal ions, temperature as well as redox reactions cause substantial changes in the conformation of peptide hydrogels. In this review, we discuss the characteristics of peptide hydrogel, factors that trigger self-assembly, mechanistic properties, route of administration and their various utility such as in biosensing, wound healing, tissue engineering, and drug delivery systems (**Table 1**).

[1]Department of Signal Transduction and Biogenic Amines, Chittaranjan National Cancer Institute, Kolkata, 700026, West Bengal, India.
†Authors contributed equally.
*email: biotechgaurav70@gmail.com

Table 1 • Definitions of diverse groups of hydrogels categorized according to the origin, cross-linking, composition and structure

Basis	Types	Definitions	References
Origin	Natural	Hydrogels built from natural polymers	[11]
	Synthetic	Hydrogels produced from synthetic polymers	
Cross-linking	Physical	Hydrogels made of non-covalent bonds such as hydrogen bonds	[9]
	Chemical	Hydrogels composed of stubborn covalent bonds	
Composition	Monopolymer	Hydrogel polymer networks created using just one type of monomer	[6]
	Copolymer	Hydrogels comprising of two or more unique monomer units, with no fewer than one hydrophilic segment, placed arbitrarily throughout the polymer network's chain	
	Multipolymer interpenetrating hydrogel	Hydrogel includes two separate, autonomously cross-linked polymer elements that have been combined into a network	
Structure	Crystalline	Hydrogels with closely packed polymer network structure	[7]
	Amorphous	Hydrogels with random network architecture	

2. Peptide hydrogels—advantages and disadvantages

Peptides are constituted by a short chain of linked amino acids and are responsible for performing diverse biological functions. Peptides make good constituents for supramolecular hydrogels as the self-assembled products are highly microporous [12], and have high water content and adjustable viscoelasticity [13]. Due to the physiochemical resemblance to the natural extracellular matrix (ECM), they are also biocompatible. Tissue engineering attempts to replicate the tissue by creating an environment similar to natural tissue including ECM and various bioactive substances. However, the intricate nature of the ECM makes this duplication process challenging. The biocompatible nature of peptide hydrogels offers methods for creating scaffolds for tissue engineering [14]. Biodegradation of these hydrogels is possible with the assistance of enzymatic and hydrolytic pathways as well as by other factors such as pH, temperature, and metal ions [15]. Furthermore, these hydrogels can conform to the morphology of the surface on which they are placed and often deform effortlessly. Peptide hydrogels, due to their unusual physical properties, are being explored for drug delivery usage [16]. The therapeutic effectiveness of drugs is hampered by their limited solubility in water. However, optimum dosage is required for optimum therapy. Consequently, several methods have been developed to maintain drug concentration at the intended site of action. Traditional methods, such as oral administration, often require high doses or repeated administration, causing hazardous side effects. Hydrogels permit spatial and temporal control of drug accessibility to cells, often concentrating the drugs at intended places thereby enhancing therapeutic efficacy by controlling drug release and minimizing hazardous toxicity by reducing the required dosage [17]. Another advantage of peptide is the ease of synthesis using simple techniques, which enables sequence-specific modifications at the molecular level [18, 19]. Moreover, these peptide hydrogels possess low immunogenicity [20]. All these properties of peptide hydrogels have collectively drawn immense attention in various biomedical fields.

However, the drawback of peptide hydrogel includes the potential need for a secondary coating and limited tensile strength and mechanical stability [21]. While the viscoelasticity of these hydrogels may be adjusted, the process of obtaining the ideal mechanical properties is challenging. Additionally, this may increase the hydrogels' sensitivity to external stimuli. Moreover, the specific loading of drugs is often troublesome and sterilization is time-consuming [2]. Another limitation of peptide hydrogel includes the fact that it cannot adhere to cells. The RGD sequence, a tripeptide motif in ECM proteins, interacts with cell surface integrin receptors and is incorporated by researchers in applications like tissue engineering and regenerative medicine to functionalize hydrogels promoting cell adhesion thereby improving bioactivity [22]. These hydrogels are often expensive, which demands a cost-effective alternative.

3. Smart peptide hydrogel—factors triggering self-assembly

Peptide hydrogels are considered "smart hydrogels" due to their capability to manipulate and tailor their properties through external environmental trigger factors. Based on these factors, peptide hydrogels can be classified [23] in the following ways:

3.1. pH-responsive hydrogel

pH is a key factor that influences molecular self-assembly of hydrogels, which makes it a potential platform for numerous biomedical applications. The conversion of liquid to gel of Fmoc-3-nitrotyrosine (FNT), a derivative of 3-nitrotyrosine (3-NT) at an extensive pH range reported by Singh et al. [24], is an example of how a trivial change in pH can result in substantial changes in gel features. The L-tyrosine amino acid that occurs naturally was used to create the gelator molecule. Tyr was first transformed into 3-NT. The modified amino acid's N-terminal was then changed to connect the Fmoc group, creating the gelator molecule FNT. FNT formed hydrogels at various pH levels.

The extent of protonation of the groups determines how soluble ionizable functions are. For instance, many peptide hydrogels display hydrogelation at pH values near the apparent pKa of the gelator because they are pH-triggered. A reverse reaction is brought by the deprotonation of a carboxylic group, which increases electrostatic repulsion [25]. In contrast, lowering the pH below the pKa results in the production of ammonium or pyridinium ions, which return the ammonium or pyridinium functionalized gels to the solution state [26]. At mildly basic as well as neutral pH, imine bond synthesis during hydrogelation is favored, while acidic pH causes a gel-to-sol transition [27]. Amphoteric gelators undergo

gelation near neutral pH, and the gels become weaker as the pH of the medium changes [28]. Due to their preference for acidic cancer cells, peptide hydrogels, which can trap medicines at higher pH levels, are excellent for delivering drugs. These hydrogels can regulate drug release, lowering adverse effects and enabling sustained local release. The pH of the media has a significant impact on the charge of peptides, which causes monomers to associate or dissociate. These hydrogels can disrupt the fibrous network, facilitating the release of therapeutic medicines laden with pKa near the pH of the tumor environment. The FER-8 peptide (FEFERFK), created by Raza et al. [29], was stable at pH 7.4 and could be used with the anticancer medication known as paclitaxel (PTX). According to findings, the hydrogel made from FER-8 allowed for drug accumulation and longer retention, which increased the anti-cancer activity of PTX.

3.2. Temperature responsive hydrogel

Temperature-sensitive hydrogels maintain a critical balance between their hydrophobic and hydrophilic residues, which in turn allow sol-gel transition. Temperature alters how hydrophilic and hydrophobic components communicate with water molecules and therefore may give rise to a shift from solution to gel state and alterations in the solubility of the cross-linked network [9]. Thermo-sensitive hydrogel is broadly divided into two major categories: negative thermo-sensitive hydrogels, which exhibit hydrogelation at a lower critical solution temperature (LCST), and positive thermo-sensitive hydrogels, which form gels at a upper critical solution temperature (UCST) [30]. Positive thermo-sensitive hydrogels turn into a solution above UCST and can contract below it as opposed to negative thermo-sensitive hydrogels, which undergo gel change above the LCST [31]. Li et al. [32] established the temperature stimuli changes in the peptide EAK16 in 2022. Increment in temperature from 25°C to 110°C and reduction back to 25°C leaves the secondary structure of L-EAK16 unchanged. However, at 25°C the D-EAK16 adopts a β-sheet conformation, and when the temperature is heightened to 110°C, it exhibits an α-helix. Peptides possess the ability to assemble into various nanostructures. This self-assembly process is due to the presence of secondary structures such as β-sheet. The thermo-stability of β-sheets corresponds to the number of hydrogen bonds [33]. The disruption of structure caused by the high temperature of thermo-responsive supramolecular peptide hydrogels prevents their investigation. Moreover, the stability of these hydrogels is regulated by hydrogen bonds. In places with high water content, these hydrogels can turn the sol-gel state around. In injectable systems, where the medication is embodied in the sol phase before transitioning to the gel phase upon injection, they are favorable [34]. These platforms are therefore promising for regulated drug release. However, temperature-sensitive systems, in which temperature is solely the stimulus, are a few of the mildest approaches and do not require additional chemical starting materials or enzymatic reactions, leading to a simpler and more convenient procedure [35].

3.3. Metal ion responsive hydrogels

The conformations and biological functions of a few peptides can be modified by coordination with metal ions. The charge of ions and the sort of aromatic system used have a crucial impact on the ion-π interactions [36]. Metal-ligand coordination bonds are formed due to the force of attraction between metal ions with electron deficit termed electrophiles and ligands that can donate electrons to an electrophile, termed a nucleophile. The charge density of the atoms can be simply altered to quickly reverse these bonds [37]. There are broadly two ways to categorize the type of ligand bound to metals. The natural ligands include residues such as tryptophan, histidine, and cysteine [38]. When these residues interact with metals, structural modifications or supramolecular arrangements might result. Artificial ligands such as bipyridine and nitrilotriacetic acid are those that trigger secondary structures to assemble into a certain type of higher order [39]. Using transmission electron microscopy (TEM), it was found that the valency of the metal ion highly influences the morphology of the self-assembled structures. Monovalent cations gave rise to helical long fibers. Divalent and trivalent cations, in contrast, produced more rigid but shorter fibers. Hydrogen bonds are responsible for the formation of these complexes and often truncate their growth. In 2020, a peptide L9 was designed by D'Souza et al. [40], which attaches to silver and slowly releases this ion in fewer amounts, solving the issue of silver toxicity. Secondary structures such as the beta-sheet assumed by L9 lead to the formation of a rigid hydrogel in response to the inclusion of silver ions. L9 has antimicrobial properties and is used for wound healing purposes. The potential of a new class of hexapeptides, E3F3 that can self-assemble in high zinc concentration, in prostate tissue-specific drug delivery systems has been investigated. These injectable peptide-based technologies enable prostate tissue-specific self-assembly. The E3F3 hydrogels exhibit the greatest mechanical strength and gelation time. Additionally, they show little cytotoxicity toward healthy liver cells. Anti-cancer medication called Docetaxel was added to the peptide hydrogel matrix, and when prostate cancer cells were cultured with them, they showed anti-cancer activity [41]. Abul-Haija et al. [42] observed the assembly of two tripeptides into a gel, which was triggered by copper ions. Supramolecular gels containing the tripeptides were not possible, either singularly or in combination. However, when exposed to copper ions, co-assembled nanotapes are organized into nanofibers thereby showing that metal coordination and ion sensitivity play a role in peptide reconfiguration. Lin et al. [43] established the self-assembly of ICG-based supramolecular system for the concurrent diagnosis along with treatment of iron overload illnesses such as hepatocellular cancer. The technique creates nano-assemblies by using Fe^{3+} coordination with sulfonic acid to speed up their clearance. This noninvasive method enables accurate localization, multimodal imaging-guided therapy efficacy, and real-time monitoring of therapeutic effects.

3.4. Redox responsive hydrogel

Supramolecular peptide hydrogels are often triggered by the reduction of disulfide bond. The disulfide bonds are cleaved by glutathione, which is an anti-oxidant residing in the human body [44]. A variety of classes of nanoparticles (NPs) is triggered by redox-sensitive linkages such as liposomal, inorganic, polymeric micelle, nanogel, and polyplex NPs.

The promotive effect of redox-responsive hydrogel on bone regeneration was reported by Yang et al. [45]. The disulfide-linked hydrogel is formed in the presence of oxygen along with concurrent addition of growth factors. Thiol-carrying molecules such as reduced glutathione (GSH), which is present in the ECM, carry out the cleavage of disulfide. Subsequently gel disintegration occurs along with the liberation of more growth factors leading to the formation of new bone. Critical physiological

functions including cell differentiation, metabolism, and proliferation depend on the maintenance of an ideal intracellular redox equilibrium. By increasing the production of reactive oxygen species (ROS), cancer cells upset this equilibrium and cause irreparable harm. GSH, a key cancer biomarker, is produced in high amounts by cancer cells as a defense mechanism. GSH is a well-known disulfide breaker that has been extensively used to create peptide-based therapeutic soft materials that are tissue-specific and redox-responsive. Controlling the self-assembly capabilities of polymeric materials has been done using H_2O_2, another redox-active substance. This form of gel is an attractive idea for the selective release of anticancer medicines [46]. Can Wu and his team [47] develop a hydrogel precursor (HCPT-SA-FFEssEE) that transforms into HCPT-peptide supramolecular hydrogel by cleavage of disulfide bond by GSH. This hydrogel was examined and an anticancer assay was carried out. The outcome was that the innovative hydrogel drug administration system showed a favorable anticancer effect and possessed a high drug-loading capacity and water solubility (**Figure 1**).

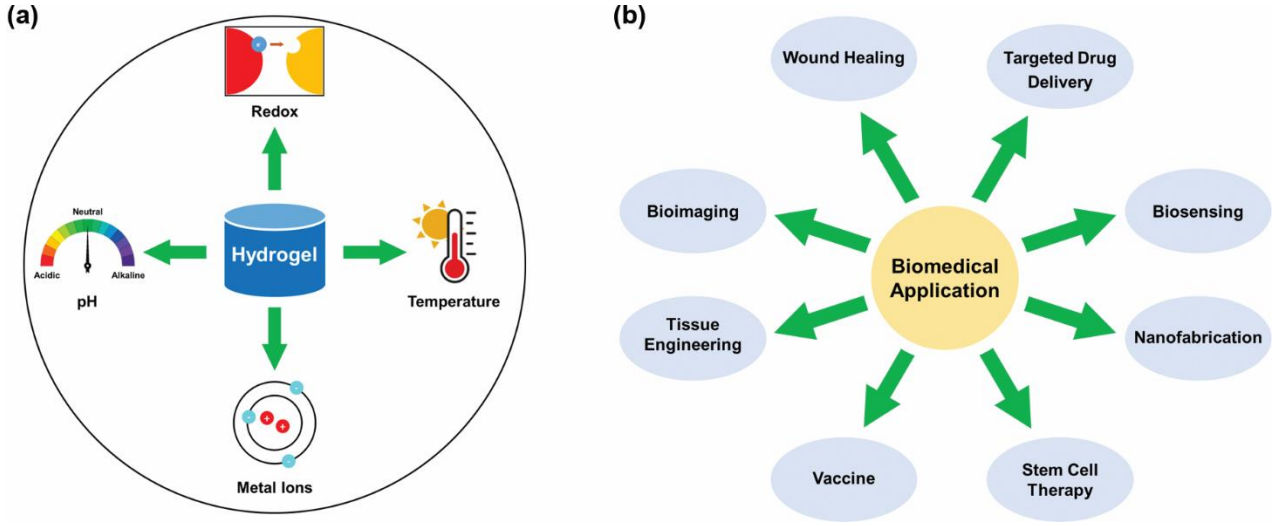

Figure 1 • (a) Different factors influencing the assembly of a peptide-based hydrogel, (b) dynamic applications of peptide-based hydrogel in the field of biomedical research.

4. Mechanical features of peptide hydrogels and their stability for drug delivery

Peptides attain several secondary structures such as β-pleated sheet, α-helix, β-turn, etc. These secondary structures thereafter assemble to construct a peptide hydrogel. The secondary structure of a peptide is governed by the amino acid residues present in the primary sequence. Consequently, hydrogelation of peptide hydrogels based on self-assembly requires the identification of the primary structure of the peptide. The following section includes the mechanical properties and stability of the peptide hydrogels due to the various secondary structures.

4.1. β-Sheet forming peptides

Diphenylalanine (FF) was discovered to be an important aggregative motif for the investigation of peptide self-assembly due to its simpler structure and flexibility. It is insoluble in organic solvents and crystallizes into semi-crystalline structures readily. The single amide bond discovered was found to be in a β-sheet-like shape. Its ability to exhibit thermal and chemical stability makes it capable of use in nanotechnology [48]. The ability of diphenylalanine to form well-organized and unique structures along with their excellent biocompatibility makes them an ingredient of Alzheimer's β-amyloid peptide and is often considered suitable for biosensing purposes [49]. Adler-Abramovich et al. [50] have documented exceptional resistance at high temperatures displayed by diphenylalanine peptide nanotubes in both dry and hydrated conditions. These nanotubes also possessed chemical stability in various organic solvents. Modification of self-assembled peptide hydrogels such as addition of aromatic groups such as 9-fluorenylmethoxycarbonyl (Fmoc) at the N-terminal was also examined. These modified dipeptides could assemble readily into hydrogel due to prominent π–π interactions for stabilization of the gel and have widespread biological applications [51]. Fmoc-FF exhibits ultra-fast hydrogelation and fibrillization kinetics. The Fmoc-FF self-assembly occurs as a result of capillary forces and surface tension [52].

Another class of β-sheet-forming peptides is nanofiber-forming peptide amphiphiles (PAs). The structure of PAs is primarily divided into four major regions such as a hydrophobic alkyl tail, a minor peptide sequence that forms intermolecular β-sheets, a charged soluble amino acid, and a bioactive moiety that serves as a signal sequence [53, 54]. A synthetic self-assembling peptide called RADA16 was fabricated by Liu et al., which was responsible for regulated liberation of the PTX, a hydrophobic anticancer drug. The RADA16-PTX hydrogel allowed controlled release of drug thereby prolonging PTX's growth-inhibiting effects on breast cancer cells. RADA16 has capacity to form β-sheet, which forms more organized structure upon increasing pH or salt addition [55]. Hydrogen sulfide (H_2S) has short half-life in fluids. As a result, the release rate of H_2S can be controlled by researchers using aromatic peptide amphiphiles (APAs) having adjustable mechanical properties [56]. The APAs had a brief IAVEEE hexapeptide linked to an aromatic S-aroylthiooxime, which served as H_2S donor [57]. Diaferia et al. [58] and co-workers examined the peptide FYFCFYF and its PEGylated variant (PEG8-FYFCFYF) produced by incorporating a cysteine residue into the $(FY)_3$ sequence; this modification favored further chemical cross-linking via thiol oxidation. The peptide that was changed to include cysteine residues allowed chemical cross-

linking via disulfide bridges, allowing it to form fibrils with a stiffer and rigid β-sheet secondary structures [59].

4.2. β-Hairpin forming peptides

β-Hairpin-type peptide hydrogel is composed of amphiphilic peptides, which consist of roughly 20 amino acid residues. These peptides are formed as a result of the chemical association of two adjacent β-sheet strands joined by hydrogen bond [60]. These peptides are called MAX1, due to the presence of parent sequence MAX1, which is constructed by two β-strands that alternately contain valine and lysine amino acid molecules [61]. The core was made of a tetra-peptide turn sequence (VDPPT), which permitted the formation of type-II turn structure. The positively charged lysine residues hinder peptide folding and self-assembly in acidic environments due to electrostatic repulsion. This leads to slow kinetics of self-assembly. However, by neutralizing the charge or covering positive charges with salt at physiological pH, intramolecular folding can be made possible [62]. Another type of hydrogel called MAX8 was formed by swapping the lysine residue with a glutamic acid residue at position 15, which allowed faster self-assembly. Both MAX1 and MAX8 form rigid hydrogels and possess self-healing property, as a result of which they are often used for drug delivery purposes [63]. Li et al. [64] created a novel peptide sequence called OE derived from MAX1 to deliver anticancer medications. MAX1 peptide sequence was modified by substituting glutamic acid for lysine at position 15, which reduced the peptide's charge, thereby increasing the stability of the gel. In order to increase the amino acid side chain's sensitivity to pH, K (isoelectric point 9.74) was substituted by O (isoelectric point 10.80) in the sixth position of the MAX1 sequence. This new peptide's full peptide sequence was "VKVKVOVK-VDPPT-KVEKVKV-NH_2" [10].

β-Hairpin peptide hydrogels have a number of distinct physical and chemical features, which are highly advantageous for the transport of cargo to a suitable location. Although these peptides possess noncovalent cross-links, the constructed hydrogel networks behave like permanent hydrogels. However, elastic gels may experience shear thinning if they are subjected to shear stress. In shear, the gel flows at low viscosity as long as the shear force is present and solidifies instantly as it was before shearing [65]. Thus, these hydrogels serve as potential drug delivery vehicles.

4.3. α-Helix forming peptides

Hydrogels that self-assemble into coiled α-helical arrangements are termed as hydrogelating self-assembling fibers (hSAFs). These helical structures may be parallel or antiparallel. These peptides have a distinct heptad repeat sequence designated as $(abcdefg)_n$, in which "*n*" represents the amount of repeats [66]. Generally, the "a" and "d" locations are hydrophobic. This serves as the coil's central core and is connected together by Van der Waals and hydrophobic interaction. The "e" and "g" comprise of polar or charged residues, which strengthen the coil through electrostatic interactions. Moreover, positions "b", "c", and "f" are often hydrophilic so that they can assume a helical conformation after being subjected to a solvent [67]. An α-helical peptide hydrogel containing this heptad sequence was designed and termed as AFD19. AFD19 showed pH responsive nature by forming a clarified self-assemble state at pH 6 and pH 10.7. Based on the conventional structure of AFD19, novel helical peptide hydrogels such as AFD36 was constructed by slight modifications, thereby forming more rigid gels. AFD36 carries a single positive charge at position 16 instead of a lysine in case of AFD19, which is sufficient to prevent the formation of large aggregates while allowing gel formation [68]. Injury of the nervous system can lead to tissue malfunction and severe illness. The repair of these tissues is difficult to accomplish. As a consequence, scientists are devising novel strategies for healing of neural tissues, which require thorough understanding of the physical and chemical composition of ECM thereby creating tailored tissue-engineered materials [69]. Another class of short oligomeric peptide is called cell-penetrating peptides (CPPs). CPPs can employ variety of entry routes for translocating across the cell membrane. The capacity of CPPS to penetrate cell membrane is contributed by their disorganized structures, which may take up a helical configuration upon contact with membrane. A series of cationic helical amphipathic peptides (CHAPs) were examined for their proficiency to invade cell membranes and deliver medications and in breast and cervical cancer cells, respectively. The CHAPs were successfully able to deliver functional methotrexate (MTX) into the cell as CHAP-MTX conjugates [70].

5. Route of administration of the hydrogel

The versatility of hydrogel's function plays a crucial role in their potential applications, encompassing the protection, targeting, and localized delivery of drug molecules. To gain a deeper insight into this different field, this section initiates through delving into the routes of drug delivery and the overall characteristics of hydrogels at the macroscopic level. We then move to the mesh scale, which controls the diffusion process and any responsive or temporal modifications. Macroscopic hydrogels, microgels, and nanogels are the three size-based categories for hydrogel delivery methods [21]. The size of the hydrogel is important since they can be used in a variety of shapes and sizes. The final defining factor in the delivery channel is the hydrogel's macroscopic structure.

5.1. Macroscopic hydrogels

To aid in trans-epithelial medication delivery, macroscopic hydrogels are often injected into the body surgically or through direct contact with the body [71]. Based on the methods they use for drug delivery, these macroscopic hydrogels can be divided into three groups: in-situ gelling gels, macroporous gels, and shear-thinning gels.

5.1.1. *In-situ* gelling hydrogels

Such peptide hydrogels can be given to patients as liquids that convert into sol-gels once they reach their bodies. The hydrogels that are produced confirm the shape of the area into which the gel was injected. There are numerous ways to achieve the sol-gel transition. One strategy is to employ slow gelling systems, wherein the process of gelation starts outside the body. The solution can be administered before it solidifies since gelation happens gradually. In systems with various gelation mechanisms, such as charge interaction [72], stereo-complexion [73], and michael addition [74], this strategy has been used. Furthermore, investigations also reveal the creation of thermosensitive hydrogels. The potential biomaterials known as injectable thermo-sensitive hydrogels have a low critical solution temperature. They go

through a change from a liquid phase to a gel phase over this temperature threshold. By infusing therapeutic compounds into the solution phase, these qualities make it simple to encapsulate them. The hydrogel then forms in place at a temperature that is physiological [21]. A pH-responsive ionic-complementary octa-peptide known as FOE (FOFOFRFE) was employed as a self-assembling agent to produce an enduring hydrogel at pH 7.4. This hydrogel formation primarily relied on non-covalent interactions, primarily driven by hydrophobic forces. It was designed to serve as an injectable carrier for delivering the antitumor drug doxorubicin (DOX). Following administration near the tumor site, the octa-peptide hydrogel disintegrated within the acidic microenvironment (pH 5.8). This disintegration leads to the transformation in the microstructure, from fiber networks to nanospheres structure. This structural change played a crucial role in achieving controlled drug release and improving the uptake of the drug by tumor cells through endocytosis pathway [75]. In an alternate study, peptide hydrogels containing emodin (EM) are first employed as injectable solutions, and then they are transformed into a semi-solid or solid hydrogels just at the point of administration site [76]. This transition is induced by external factors like light, temperature, and pH. In this specific instance, the gelator employed was the RADA16-I peptide, known for its ionic complementary self-assembling properties. Notably, the in-situ development of RADA16-I-EM hydrogels resulted in a significant slowing of tumor growth and a lessening of EM's damaging effects on healthy cells [76].

5.1.2. Shear-thinning hydrogels

Some hydrogels have the ability to externally pre-gel before being injected into the body, leveraging shear tension as the trigger [77]. Due to their transient physical cross-links, these hydrogels have fluid-like characteristics with modest viscosity upon injection but quickly restore the initial rigidity once the impact of shear is eliminated. Because of the dynamic interaction between pro-assembly forces like hydrophobic contacts, electrostatic interactions, and hydrogen bonding and anti-assembly forces like solvation and electrostatic repulsion, these physical cross-links are reversible [78]. Simonovsky and Miller [79] have recently revealed a variety of novel hairpin peptides that can bind to Zn^{2+} ions and create structures that resemble fibrils [80]. In order to develop potential binding sites for Zn^{2+} ions, they created nine unique peptides based on the MAX1 peptide by altering Lys and Val residues to His and Cys residues [62]. The peptide's self-assembly method and, in turn, its structural features were impacted by the placement and quantity of Cys and His receptors in the Zn^{2+} docking site [79]. The Zn^{2+} binding site of peptides containing three or four His residues produced stiffer and fewer twisted nanofibers. On the other hand, peptides having 2, 3, or 4 Cys residues at the Zn^{2+} binding region resulted with more turned flexible, and fragile nanofibers [79]. Even though the MAX1 peptide group is well known for its shear-thinning properties. For instance, Wei et al. [76] created an array of reactive aromatic dipeptides that may generate hydrogels that are shear-thin and have tenable mechanical characteristics as well as the capacity to heal themselves. Their findings showed that the mechanical properties and self-healing capacities of these hydrogels are strongly influenced by a synergistic interaction involving hydrophobic and hydrogen bond interactions. While enhancing hydrogen bonding interaction, there is an enhancement of the self-healing process and hydrophobic interactions among molecules, which promotes mechanical stiffness [76].

5.1.3. Macroporous hydrogels

In this method, injectable hydrogels are synthesized in order to form large hydrogels containing interconnecting pores that are capable in reversible mechanical collapse and recovery. During injecting a gel through needle, water came out of these pores, causing the gel to compress and pass through the needle. The hydrogel then quickly returns to its original shape inside the body after extrusion and elimination of the mechanical restriction [81].

5.2. Microgels and nanogels

Due to their small size, they can be injected using a needle and they offer a substantial surface area for bio-conjugation. This feature facilitates easy natural elimination and enhanced penetration through tissue barriers [82]. Microgels and nanogels, which are recently emerging as promising biomaterials with substantial potential in numerous biological areas, including controlled drug release, are created simply by the self-assembling of short peptides. A prime instance includes the work of Lyu et al. [83], who developed stimulus-responsive short peptide nanogels that are for controlled intracellular drug release. They introduced a P-glycoprotein (P-gp) inhibitor and doxorubicin-containing self-assembling nanogel technology that is responsive to the environment. This nanogel exhibits acid sensitivity, allowing for drug release, while also impeding P-glycoprotein's efflux function. Consequently, this approach successfully combats multiple drugs that are used in cancer treatment, improving outcomes in the field of cancer therapy [83].

5.3. Local drug delivery by peptide-based hydrogel

When choosing the method for delivering the gel, it's important to consider the bio-adhesive characteristics. It's worth noting that hydrogels face limitations in adhering due to the presence of two biological limitations, namely the epithelium of intestine and mucosa. Numerous efforts have been made over time to create bio-adhesive hydrogels for local medication delivery. Tang et al. [84] investigated the capabilities of self-assembling peptide-based concentrated solutions and hydrogels as candidates for enhancing drug delivery to mucosal surfaces, such as those found in the oral, nasal or ophthalmic areas. Building upon prior research by Zhang et al. [85], this group designed a set of self-assembling peptides, each consisting of eight amino-acids arranged in alternating hydrophobic (away from water) and hydrophilic (towards water) sequences. This structure made it possible to build hydrogels with specialized qualities. In their investigation into these hydrogel's properties, they assessed their suitability as muco-adhesives for localized delivery for drug. They examined the release of two pharmaceutical drugs: lidocaine, which was found to be soluble in the conditions applied, and flurbiprofen, which was insoluble, with a focus on the octa-peptide Phe-Glu-Phe-Glu-Phe-Lys-Phe-Lys [84]. The outcomes showed that the samples' rigidity increased as a result of adding a dose of lidocaine. Generally, drug retention was not favored due to the like charges of both the drug and the peptide. On the other hand, greater sample rigidity was associated with better medication retention. The samples' mechanical characteristics were unaffected by the addition of flurbiprofen. However, samples with lower mechanical integrity were less resistant to physical erosion brought on by the flow of a salt solution when the medication was present. On the other hand, when the hydrogels' basic mechanical properties were strong enough,

adding flurbiprofen greatly improved resistance of hydrogel against corrosion. The rigidity of the peptide-based hydrogel played a pivotal role in maintaining its structural integrity during usage and after adhesion. Tailoring the peptide to improve muco-adhesive properties is possible, depending on the specific application area of the hydrogel. Designing charged peptide-based gels, for instance, has potential for extending ocular residence duration for applications with negatively charged mucosa by improving muco-adhesion through electrostatic interactions with negatively charged mucin [84]. Recently, Liu et al. [16] developed supramolecular hydrogels for prolonged ocular drug delivery using peptides with cationic groups as molecular hydro-gelators. Additionally, the simultaneous delivery of timolol (1-(*tert*-butylamino)-3-[(4-morpholine)-1,2,5-thiadiazol-3-yl)oxy]-2-propanol) and brimonidine (5-Bromo-*N*-(4,5-dihydro-1H-imidazol-2-yl)quinoxalin-6-amine) to treat glaucoma using a self-assembling peptide hydrogel was also described by Taka et al. [86].

6. Biomedical application

Peptide-based hydrogels have countless effects and implications within the realm of biomedicine [87] (**Table 2**).

Table 2 • Different biomedical applications of peptide-based hydrogels

Field of application	Applications	References
Targeted drug delivery and cancer immunotherapy	PXT-loaded hydrogel demonstrated significant drug presence at tumor locations and prolonged retention. In cancer immunotherapy, hydrogels with DOX and DPPA-1, triggers anti-tumor immunity, amplifying T-cell-mediated immune responses, and reducing adverse effects.	[29, 88]
Wound healing	IKFQFHFD, an artificially designed octa-peptide with antimicrobial properties, can self-assemble into a hydrogel and enhance the healing of diabetic wounds infected with MRSA.	[89]
Tissue engineering	An active hyaluronic acid hydrogel linked with gelatin inhibits the development of reactive oxygen species resulting in the cartilage reconstruction.	[90]
Biosensing	Detection of matrix metalloproteinase-7 or MMP-7 as an acceptable biomarker enzyme for identifying colon cancer.	[91]
Bioimaging	An amphiphilic peptide hydrogels and a fluorophore can be used to create supramolecular fluorescent hydrogels. This device enables bio-imaging and specific cancer detection.	[92]
Stem cell therapy	Surging in neurite production, neuronal differentiation, and gene expression linked to dopaminergic neurons in the NSC (neuron stem cell) culture by the application of double-layered alginate hydrogel.	[93]
Nanofabrication	The production of lengthy, ultra-thin copper (CuS) nanowires utilizing peptide hydrogel as a template.	[94]
Vaccine	Delivery system for DC-based vaccine in EG7-OVA tumor model.	[95]
Molecular imprinting	Using the molecular imprinting technology to demonstrate the considerable improvement of the catalytic activity of a peptide recombinant hydrolase.	[96]

6.1. Targeted drug delivery and cancer immunotherapy

Drug delivery systems possess the capability to direct drugs toward specific tissues, reduce adverse effects, address challenges related to solubility and toxicity, and be customized to exhibit suitable immunogenicity and metabolic stability [97]. Particular treatments enable localized distribution of medications, thereby effectively minimizing undesired general side effects. As nanotechnology progresses, numerous systems have emerged, employing either active or passive methods to specifically deliver medications to particular cells and tissues [98]. The process of "active targeting" entails attaching chemicals that target certain tissues that are important to the outermost layer of NPs [99]. Targeted cancer therapy is one of the poly-peptide-based nanosystems, which have received a great deal of attention as a possible means of accomplishing targeted delivery of a variety of payloads [97]. Self-assembled peptide nanostructures have the ability to change surface ligands, have highly adaptable physicochemical properties, and are highly biocompatible. These characteristics have made them an excellent option for applications involving specific administration of chemotherapeutic drugs [100–102]. There has been a great deal of investigation into the potential applications of self-assembles peptide-based drug delivery mechanisms, including hydro gels, fibers, and NPs, in specific cancer therapy. Raza et al. [29] produced a pH-sensitive hydrogel using the FER-8 peptide to transport PXT, providing an illustration of a pH-dependent mechanism made of self-assembling peptides. In mice expressing the H22 mutation, this PXT-loaded hydrogel demonstrated significant drug presence at tumor locations and prolonged retention. Drug is released during hydrogel disintegration in an acidic environment of the tumor microenvironment. This technology has shown remarkable promise for sustained and localized administration of drugs for specific cancer therapy [29]. A recent instance of advanced and versatile photo-thermal therapy, as showcased by Zhao et al. [103], involved the utilization of a hybrid hydrogel comprising Ag_2S quantum dots embedded within a peptide hydrogel containing the RGD motif (PC_{10}ARGD). Through exhibiting tumor necrosis and excision after laser irradiation and leaving behind dark scars at the tumor locations, these hybrid nanogels demonstrated their potential for PTT. Additionally, this nanosystem has shown potential for applications in photo acoustic imaging targeted NIR fluorescence imaging [104], and PTT in the field of cancer therapy [103].

Cancer immunotherapy is a new field of study that uses immune-modulatory drugs to boost mammalian immune system activity,

which stops and destroys cancer cells [105–107]. The favorable attributes of self-assembled peptide structures, including their bioavailability and biodegradability, coupled with their ability to release drugs in a controlled manner, position these structures as promising candidates for application in this field of research. Additionally, supramolecular peptide architectures offer a flexible way to individually and dynamically modify the body's immune response through their innate actions, either as immunological regulators or immune stimulants [107]. Recent advancements have introduced a range of self-assembled peptide-based supramolecular structures for delivering drugs to tumors [108]. In a study, Qi et al. [109] formulated injectable hydrogels loaded with DOX that exhibited an antiparallel β-sheet structure. These hydrogels were created using a hexapeptide hydrogelator named FEF3K, maintaining string connections between the filaments, resulting in continuous DOX absorption. This method significantly suppressed tumor growth in breast cancer mouse models while notably mitigating the adverse effects linked to the administration of free DOX. A short-chain d-peptide antagonist focusing on a protein called programmed cell death-ligand-1 and an enzyme inhibitor of indoleamine 2,3-dioxygenase were carried by self-assembled peptide NPs to provide successful combination treatment for cancer. In this research, an active chemical called 3-diethylaminopropyl isothiocyanate was co-assembled with a peptide substrate of MMP-2 to create amphiphilic peptide nanostructures that contained DPPA-1 (diphenylphosphoryl azide-1). In reaction to an acidic environment and significant amounts of MMP-2 at the tumor location, the NP cargo was released. The simultaneous inhibition of immunological barriers and interfering with Trp metabolism brought about by the administration of these NPs increased the number of cytotoxic T cells that infiltrated the tumor, effectively slowing the growth of the melanoma tumor [110]. In a recent investigation, NPs were designed to specifically target αvβ3-integrin receptors, which are typically overexpressed on the surface of tumor cells. These NPs were created by linking a self-assembled pro-apoptotic peptide with RGD (arginine-glycine-aspartic acid) and these serve as near-infrared fluorescent dyes. Notably, U87MG glioblastoma cells readily absorbed these NPs, indicating the possibility of using them as a theranostic agent to treat glioblastoma brain tumors [111]. In another strategy, Liu et al. [88] have created an injectable hydrogel, HA-DEG/UPy copolymer supramolecular hydrogel or HDU, designed for the localized delivery of DOX and DPPA-1. This hydrogel, when locally injected, allows gradual release of encapsulated DOX, effectively targeting tumor cells and triggering immunogenic cell death (ICD) to stimulate the body's antitumor immune response. Simultaneously, the DPPA-1 peptide within the hydrogel functions to regionally hinder the PD/PD-L1 interaction, thereby enhancing T-cell-mediated immune responses. The treatment resulted in improved infiltration of cytotoxic CD8+ T-cells into the tumor and notably increased levels of TNF-α and IFN-γ secretion. These combined effects observed in animal studies showed a synergistic therapeutic effect. As a result, this injectable peptide-based hydrogel exhibits potential to enhance the success rate to immunotherapy while reducing its systematic side effects.

6.2. Wound healing

Hydrogels are considered to be as promising options for wound dressings because they can create a humid atmosphere conducive to wound dressings [11]. Due to their vast range of possible uses, peptide-based hydrogels have attracted the most attention among the numerous forms of hydrogels in the disciplines of medicine and biomaterials [112]. For an instance, MAX1, a representative β-sheet peptide, has the ability to self-assemble into an antimicrobial hydrogel when placed in DMEM, without the addition of chemical linkers [113]. Additionally, IKFQFHFD, an artificially designed octa-peptide with antimicrobial properties, can self-assemble into a hydrogel and enhance the healing of diabetic wounds infected with MRSA [89]. The use of peptide-based hydrogels, which do not rely on antibiotics or chemical linkers, represents a novel approach in the development of antimicrobial wound dressings [114]. Xiong et al. [115] introduced a hyaluronic acid (HA)-based hydrogel incorporated with Fe^{3+} ions and an antimicrobial peptide modified with dopamine. This hydrogel exhibited characteristics conducive to photothermal-assisted wound healing in the context of bacterial infections. The antimicrobial properties of the DAP peptide were intrinsic, as it served as a scavenger for ROS. Additionally, by creating Schiff's base and covalent interaction between aldehyde HA and Fe^{3+}, respectively, it added to the structural stability of the hydrogel. Findings from research conducted *in vitro* and *in vivo* experiments supported the idea that this hydrogel speeds up the healing of wounds at infected locations. This showed the extraordinary potential of hydrogels with photothermal and antioxidant attributes to treat wounds and treat bacterial infections [116].

6.3. Tissue engineering

Tissue engineering is the biomedical field of restoring and substituting damaged tissues by utilizing artificial biocompatible constructs compromising cells, biomaterials, and bioactive molecules. These constructs aim to replicate the desired tissue repair and regeneration [117]. Hydrogel material having 3D cross-linked macromolecular networks is capable of trapping a substantial amount of water molecules, exhibiting strong potential as biomaterial candidates in the field of tissue engineering [118]. Biomaterials have the ability to provide 3D scaffolds that closely mimic the characteristics of the natural ECM in the body. These scaffolds interact with specific cells, influencing their behaviors and facilitating the synthesis of new tissue and organ. Biomaterial scaffolds play a pivotal role in advancing tissue engineering development and applications [119]. Hydrogel scaffolds have a great deal of opportunity for tissue repair in a variety of settings, including the regeneration of cartilage, bone marrow, and heart tissue. For instance, in animal models, the 3D printing of collagen-chitosan hydro gel reduces scarring, promotes cavity formation, and improves nerve fiber repair and restoration of function [120]. Another example is the use of HA, fibrin, and alginate as a common element in 3D printing for the restoration of peripheral nerve tissue. [121]. In addition to this, HA-cellulose hydrogels have demonstrated the ability to repair central nerves [122]. In a different investigation, mesenchymal stem cells were enclosed in a hydrogel that had been cross-linked using choline oxidase and horseradish peroxidase. This hydrogel demonstrated a surprising ability to increase cellular viability, encourage neural development, and make it easier for the loaded mMSCs to release neurotrophic compounds. This property allowed it to enhance the recovery of neurological function in mice with severe brain lesions and stimulate the survival and multiplication of native neural cells [123]. A chondro-spheroid hydrogel composed of gelatin methacrylate that has been cross-linked with HA methacrylate has been studied by Wang et al.[124]. In an *in vivo* setting, this hydrogel was found to improve

cell growth, aggregation, and morphological traits. Their findings imply that this 3D cell-rich tissue may have potential for use in connective transplantation. This method of gelation can also be used in conjunction with carboxy-methyl cellulose, CMC, and alginate as biological inks for 3D printing human joint meniscal scaffolds. These scaffolds were shown to be suitable for tissue engineering of cartilage because they were able to boost the collagen outflow and cell growth of MG-63 sarcoma [125]. Furthermore, an active HA hydrogel that is covalently connected to gelatin has also been shown by Shi et al. [90] to be able to inhibit the development of ROS, which in turn affects cartilage reconstruction. A temperature-sensitive peptide hydrogel with IKVAV was created by Chai et al [126]. It has a reliable 3D porous structure, good biological activity, and quick (de)swelling times. The scientists used this scaffold to treat spinal cord injuries, and the results showed increased angiogenesis, decreased glial scar tissue formation, and suppression of keratinocyte adhesion and differentiation. According to research by Bordini et al. [127], even in the presence of an inflammatory microenvironment, a gelatin hydrogel modified alongside nanotubes loaded with Dex (dexamethasone) may be able to induce bone regeneration. Additionally, they have developed 3D-printed scaffolds made of gelatin and sodium alginate, which are enriched with nano-attapulgite. These scaffolds possess the intricate structural complexity required for bone regeneration. They have demonstrated the ability to support the formation of new bone tissue (osteogenesis) by mesenchymal stem cells (mMSCs) and effectively repair defects in the rabbit tibia plateau [128]. Furthermore, Banwell et al. [129] present a unique application of self-assembling hydrogels: hSAFs in tissue engineering. These hydrogels are composed of linear peptides, which are completely α-helical in structure. They concluded that hSAFs effectively facilitate the growth and differentiation of rat adrenal pheochromocytoma cells over extended periods in culture like matrigel does.

6.4. Biosensing

Peptide hydrogel biosensors have gained more attention recently. The remarkable response of these sensors to external conditions like temperature and pH has attracted interest. Additionally, they provide benefits including great cell adhesiveness, a proven chemistry for structural alterations, sustainable biochemical and mechanical robustness, resistance to fouling, the capacity for self-healing, and adaptable viscoelastic characteristics [130]. Gagni et al. [131] used YF-Q11 peptide-based hydrogel to bind biomolecular probes in the context of viral detection. They used this hydrogel-biological probe combination to generate 3D arrays on poly(methyl methacrylate) slides. After that, they assessed the biosensor's immunodiagnostic capabilities for identifying Zika virus strains in human serum samples. Additionally, this hydrogel is a simple and in-expensive biosensors as it can be printed on poly-methyl-methacrylate plates [131]. Zhang et al. [91] created a recent electrochemical sensor for the accurate detection and collection of tumor biomarkers in biological samples. They found matrix metalloproteinase-7 (MMP-7) as an acceptable biomarker enzyme for identifying colon cancer. The result of experiment shows that the signals from the sensor increased the level of MMP-7.

6.5. Bioimaging

In the field of biomedicine, bioimaging holds paramount importance because it helps in visualizing biological processes and biological materials in multi-dimensional aspect within living organisms. This method is well-known for its non-invasive nature and ability to monitor biological events in real-time by fusing cutting-edge materials with imaging probes [132]. It provides useful information on biological functions, signaling networks, and the impact of different chemicals on humans [132]. Lately, there has been an increasing fascination with employing bioimaging agents of supramolecular fluorescent hydrogel (SFH) in various biomedical applications, encompassing both treatment and diagnosis. These probes are favored for their biocompatibility, biodegradability, responsiveness to stimuli, and 3D cross-linked structures [133]. Hydrogels made of peptides are considered as outstanding biomaterials with considerable benefits for bioimaging applications [134]. Numerous researches have highlighted peptide-based hydrogels advantages in the field of bioimaging. Molecular-based peptide hydrogels are exceptional due to their biosafety and absorption efficiency, thus they capable of efficient renal clearance as well as capable of crossing a numerous physiological barriers. Additionally, peptide hydrogels can be programmed to react to many stimuli, including pH, light, temperature, and antioxidant enzymes [135–137]. These properties suggest that some stimuli may be able to cause peptides to self-assemble, resulting in the *in-situ* creation of peptide hydrogels. This may increase the quantity of imaging chemicals in specific regions, enabling advanced, specific, and accurate bioimaging [138]. Additionally, peptide hydrogels can protect bioimaging chemicals from cellular excretion, extending their durability and consistent bioimaging [17]. As a result, peptide-based hydrogels can be extremely useful components in applications related to diagnostics. According to a study by Gao et al. [92], amphiphilic peptide hydrogels and a fluorophore can be used to create SFHs. This device enables bio-imaging and specific cancer detection. Along with acting as imaging probes, these hydrogels have the ability to react to particular stimuli found in the cancer microenvironment. They can also act as medication carriers. Moreover, Fan et al. [139] discovered the creation of Trp-Phe dipeptide NP3 (DNPs), which can alter the peptide's intrinsic fluorescent indication from the ultraviolet to the visible spectrum. These DNPs recognize the overexpression of MUC1 proteins on the membrane of human carcinoma epithelial cells A549 in order to target and sense malignancy.

6.6. Stem cell therapy

Stem cells (SCs) are specific cells capable of dividing in a continuous manner and are able to convert into different cell types within a particular tissue or organ. Additionally, they can be used as means of transmitting intricate signals. SCs come in different types for an instance embryonic and adult SCs. Adult SCs can be typically observed in specific ECM environments, where they proliferate, differentiate, and specialize as needed [140]. The concept of SC therapy was first explored successfully in 1998 with the creation of embryonic stem cells (ESCs) [141]. SCs have become the subject of significant study in a number of areas, including tissue engineering, the treatment of heart illness, cancer, osteoarthritis, diabetes, and treatment for neurological disorders. According to these findings, SCs are highly promising as therapeutic possibilities for rejuvenating treatments [142]. A novel approach using a double-layered alginate hydrogel was suggested by Qiao et al. [93]. The outer layer was altered using the Crypto-1 antibody in order to facilitate the delivery of neural stem cells (NSCs) and MMP along with RGD polypeptides were grafted onto it. The RGD peptide-immobilized inner layer

promoted the growth of NSCs. Furthermore, by blocking Crypto-1, the outer layer application of a Crypto-1 antibody improved the *in vitro* development of dopaminergic neurons. After the inflammatory reaction subsided, transplanted SCs secreted MMP, which cleaved the MMP polypeptide in the inner layer and caused NSCs to migrate to the outer layer. As a result, there was a notable increase in neurite production, neuronal differentiation, and gene expression linked to dopaminergic neurons in the NSC culture on this hydrogel formulation. Furthermore, hematopoietic cytokines and a self-assembling peptide hydrogel were presented by Shan et al. [143] to create a 3D scaffold for the *in vitro* cultivation of hematopoietic cells from small-scale pluripotent stem cells (PSCs). First, they showed that the mouse PSCs (mPSCs) in the hydrogels were able to induce hematopoietic differentiation, which resulted in the apparent expression of certain markers like CD41, CD45, and c-kit. The differentiation of mPSCs was aided by this 3D environment. Furthermore, mPSC differentiation resulted in the generation of multipotent progenitor cells, and within this system, hematopoietic stem cells (HSCs) showed promise for lymphocyte cell differentiation. Additionally, IKVAV-PA gels (peptide based hydrogels) were injected into the temporal bone of a human cadaver and showed promising results for the delivery of SC in a clinical setting. Therefore, it is recommended to combine injectable self-assembled PA gels with ESC transplantation to provide the ideal microenvironment for inner ear regeneration [144] (**Figure 2**).

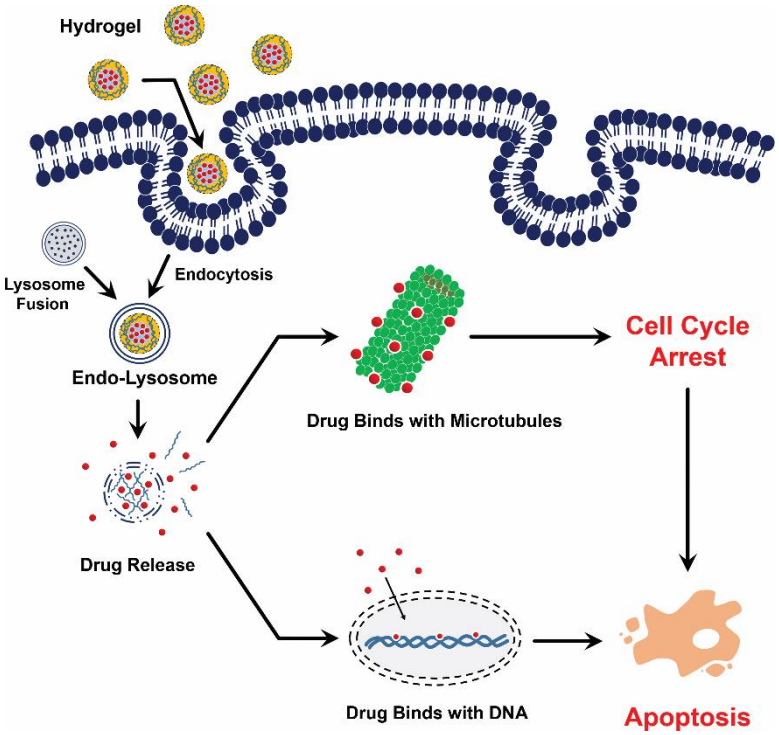

Figure 2 • Pictorial representation showing the targeted drug delivery through peptide-based hydrogel into cancer cells.

6.7. Template for nanofabrication

Peptide hydrogels have the capability to spontaneously create bio-inspired structures through self-assembly, resulting in the formation of both two dimensional and 3D structures. These architecture act as templates or scaffolds for generating a wide range of nanostructures for instance particles, tubes, wires, nanoreactors, ribbons, and more, utilizing different types of materials such as silica, polymers, and metals [145]. As an illustration, peptide nanotubes filled with water can act as templates for producing nanowires and structures made of metals or polymers. Additionally, through this manufacturing method, the creation of fascinating composite materials becomes possible, like nanowires composed of metal-peptide-metal with distinctive electromagnetic characteristics or peptide nanotubes featuring platinum NPs affixed to their surfaces [146]. The production of lengthy, ultra-thin copper (CuS) nanowires utilizing peptide hydrogel as a template was also demonstrated by Ahmed et al. [94]. The self-assembly process was started with copper (II) ions using a new hairpin peptide made up of four histidine residues. CuS wires were produced, and the near-infrared laser irradiation caused them to demonstrate a thermo-effect [147]. Another work used a simple lysine-based peptide amphiphile attached to a C16 hydrophobic tail to create a self-assembling nanofiber hydrogel that was used as a template to create mesoporous single-walled silicon-based nanotubes [94]. These hydrogel templates make it possible to create homogenous nanostructures or microstructures in different range of sizes and in various form that can be used for encapsulation of drugs as well as release of pharmacokinetics [148]. Adhikari and Banerjee [149] showed how to create silver (Ag) nanoclusters in situ while exposed to sunlight using ultrashort peptide-based hydrogels to be as templates. They used an extremely short peptide called Fmoc-Val-Asp-OH to make transparent and durable hydrogels for encapsulating Ag ions. Under physiological pH, these hydrogels are able to generate fluorescent Ag nanoclusters on their own. The aspartic acid residues in the peptide had carboxylate groups that decreased the Ag ions when they were exposed to sunlight [150].

6.8. Vaccines

Vaccines are designed to strengthen the immune system's natural defenses against foreign invaders. Lately, peptides with the ability to self-assemble into certain nano-architectures have demonstrated significant promise as cutting-edge biomaterials for the creation of vaccines [81]. In addition to this due to their large-scale, cost-effective production, biocompatibility, and

relatively high levels of stability and activity, peptide-based hydrogels provide immune adjuvants as widely accepted alternatives [81]. According to a study by Rudra et al. [151], ovalbumin was chemically attached to self-assembled Q11 peptides in order to produce a chemical adjuvant that elicits an immune response. Later, Huang et al. [152] created a number of breast cancer vaccines and attached Q11-based peptides to them. When conditions are favorable, the Q11 segment assembles itself into fibers, acting as the vaccine's adjuvant and carrier. The generation of antibodies targeting human breast tumor cells is a result of the immune system being successfully stimulated by these hydrogel-vaccine systems. To improve humoral immune responses, Wang et al. [153] used Nap-GFFpY-OMe peptide-based hydrogels containing immune adjuvant ovalbumin (OVA). A greater number of antibodies and pertinent cytokines were produced as a result of the entrapped OVA. These formulations can be created for protein-based vaccines in cancer immunotherapy due to the strong biocompatibility and biodegradability of their hydrogels. The MUC1 antigen was chemically coupled with the polypeptide Nap-GDFDFDYDK by this research team to produce anticancer hydrogel vaccines that could elicit immune responses that are cellular as well as humoral [154]. A few researches have been done on hydrogels that are capable of triggering immunological reactions. For instance, Xing et al. [155] made significant contributions to the field of injectable supramolecular hydrogels by employing peptides to co-assemble poly-L-lysine (PLL) and FF dipeptide via electrostatic coupling. These Fmoc-FF/PLL-SH hydrogels function as an adjuvant because of their nanofibrous structure, which resembles natural fimbrial antigens in a α-helical conformation. These hydrogels, when applied around a tumor site, stimulated T-cell responses and effectively inhibited tumor growth without the need for further adjuvants or antigens. Interestingly, in this case, the antigen is the tumor cells themselves, which elicit an immune response. Furthermore, according to Yang et al. [95], both endogenous and exogenous DCs were successfully drawn to and activated by a nanofibrous scaffold made of a hydrogel based on the RADA16 peptide and encapsulating bone marrow-derived DCs, model antigen ovalbumin (OVA), and anti-PD-1 antibody. As a result, DC migration to the lymph nodes was boosted, which strengthened the immune response against EG7-OVA tumors and made it more targeted.

6.9. Molecular imprinting

Molecular imprinting is a technique used to create structures with extremely precise chemical arrangements, allowing them to selectively recognize and bind to specific target molecules even when they are very similar in structure, achieving enantiomeric resolution [156]. This procedure includes cross-linking monomers while a template molecule is present. The template molecule is then removed to leave empty spaces in the material that the desired molecule can fill. Molecular imprinting not only generates sites for target recognition but also results in materials that respond to stimuli. Numerous biomedical domains, such as chemical sensing, immunoassays, imitating antibodies, catalytic procedures, and synthetic enzymes, are interlinked with the applications molecular imprinting [157]. In particular, molecularly imprinted polymeric hydrogels have been extensively researched for their potential in drug delivery, offering advantages such as high drug loading and improved control over drug release. They have also shown promise in tissue engineering [96]. Wang et al. [96] used the molecular imprinting technology to demonstrate the considerable improvement of the catalytic activity of a peptide recombinant hydrolase in their study. The improvement was astounding; it was around seven times better than what was seen in a co-assembled mechanism. To arrange the residues associated with catalysis (Ser/His/Asp) inside the Fmoc-FF peptide, they used p-nitrophenyl acetate (NPA) as a template. The combination resulted in nanofibers. Notably, this marked the first application of the molecular imprinting method for creating enzyme mimics using self-assembling peptides as supramolecular structures [158].

7. Conclusion and future perspective

Supramolecular chemistry has made significant progress during the past two decades, both in terms of conceptual knowledge and practical applications. Once a coincidental discovery, hydrogelation is a fairly known phenomenon that allows the appropriate construction of self-assembled systems with customized structure and features. Although the success has increased significantly in this area over the past ten years, there are still many factors that need to be explored [159]. Our review underscores the multifaceted nature of peptide hydrogels and their myriad applications. Peptide hydrogels have evolved as a promising approach in the field of biomedicine due to their distinct secondary structures, which directs their mechanisms, their ability to react to various physical and chemical triggers such as temperature and pH which enable them to be fine-tuned and tailored for specific applications in various diagnostic platforms. These peptide hydrogels are highly biocompatible, which allow them to serve as potential avenues in the realm of biomedical research, for example, in drug delivery, tissue engineering, and regeneration. The future of peptide hydrogels holds numerous challenges that need to be addressed by the researchers. Peptide hydrogels are sensitive to environmental stimuli, which makes the extension of their shelf life complex. These hydrogels are often expensive, which demands for a cost-effective alternative that can be distributed on broader scale. In order to develop as a real-life solution, these peptide hydrogels need to fulfil certain regulatory parameters such as clinical trials, which may be labor intensive [117]. In forthcoming investigations, hybrid materials capable of amalgamating advantageous traits from various material categories, including chemically cross-linked ones, could be highly appealing objectives. This potential could lead to the creation of novel stimuli-responsive hydrogels that react to factors such as light, temperature, pH, and electric fields. Therefore, the rapid advancement in polymer development is crucial in the field of biomedical applications. However, the practical application of peptide-based injectable hydrogels encounters obstacles due to their relatively limited mechanical strength and stability. Moreover, it is crucial to consider the release profile of biologics from hydrogels to further progress their application. The future direction of hydrogel development involves customizing the structure and functionalities of peptide-based hydrogels to meet diverse needs across various fields. This requires designing rational two-dimensional and 3D peptide structures by controlling their hydrophobic interactions, π–π stacking, and hydrogen bonding [160]. Additionally, peptide-based hydrogels can serve as frameworks for *in vivo* biomineralization, leading to the creation of biomimetic mineralized tissues such as bone or teeth. Future studies may explore methods to regulate the speed, structure, and mechanical characteristics of the mineralization process in these hydrogels

for applications in tissue engineering and regenerative medicine. Overall, the prospects for peptide-based hydrogels in *in vivo* applications seem promising, as ongoing research enthusiasts aim to enhance their capabilities, improve their performance, and facilitate their integration into clinical settings for various biomedical purposes [161]. As we look into the future, we expect these hydrogels to make remarkable developments, which will revolutionize numerous aspects of biomedicine. These hydrogels possess the ability to emerge as a cornerstone of biomedical innovation thereby giving rise to a brighter and healthier future ahead of us.

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Authors contribution

Conceptualization, G.D.; validation, G.D.; investigation, S.G. (Srestha Ghosh), S.C. and S.G. (Subhabrata Guha); writing—original draft preparation, S.G. (Srestha Ghosh) and S.C.; writing—review and editing, S.G. (Subhabrata Guha); supervision, G.D.; funding acquisition, G.D. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Data supporting these findings are available within the article, at https://doi.org/10.20935/AcadMatSci6183, or upon request.

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The authors declare no physical samples were used in the study.

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