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# Water-Soluble Biocompatible Polymers from Sustainable Amino Acid Moieties for Biomedical Applications

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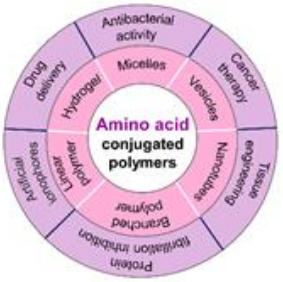
**Abstract:** Amino acids have emerged as sustainable and versatile building blocks for the creation of functional polymers. Harnessing their intrinsic structural diversity and biological relevance enables the design of unique, well-defined, biocompatible, and highly tailorable macromolecules. Beyond their natural abundance, the exceptional biocompatibility of amino acid-derived polymers positions them as promising candidates for a wide spectrum of biomedical applications. Moreover, the diverse reactive functionalities of amino acids (such as carboxylic acid, amine, thiol, and hydroxyl groups) provide a powerful synthetic toolbox, supporting a broad range of polymerization strategies from step-growth to chain-growth mechanisms. This review highlights the recent developments (2015-present) in the synthesis of amino acid-conjugated polymeric architectures and their biomedical applications. By bridging molecular design, polymer chemistry, and bio-functionality, we highlight the transformative potential of these bioinspired materials and anticipate their pivotal role in shaping the next generation of sustainable and therapeutic polymer platforms.




**Keywords:** *Amino acid, RAFT polymerization, stimuli-responsive polymers, biocompatibility, antibacterial, drug delivery*

## Contents



## 1. Introduction

Natural amino acids, the fundamental monomeric units of proteins, are indispensable to life for the maintenance and regulation of all living systems, providing the molecular foundation for cellular architecture, functional organization, and the complex biochemical processes.[1,2] Proteins possess distinct three-dimensional conformations that are critical to their biological function, as their structure governs molecular interactions, target binding, and the execution of specific cellular processes essential to life (Figure 1).[3] To emulate the structure and function of natural proteins, researchers have developed amino acid-based synthetic materials to mimic their remarkable specificity, conformational flexibility, and functional efficiency in both biological and technological applications.[4] In this context, amino acid-derived polymers have attracted significant interest in biomedical research due to their unique properties, such as superior aqueous solubility, inherent self-assembly capabilities, stimuli-responsive behavior, and outstanding biocompatibility.[5,6] The inherent biological activity of amino acids, largely attributed to the presence of a chiral centre (excluding glycine), positions them as highly attractive candidates for use as foundational monomers in the development of functional polymeric materials.[7]

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The diverse chemical functionalities of amino acids, such as carboxyl (-COOH), hydroxyl (-OH), amino (-$NH_2$), and thiol (-SH) groups, render them highly versatile and attractive moieties for polymer functionalization (Figure 1).[8] The initial

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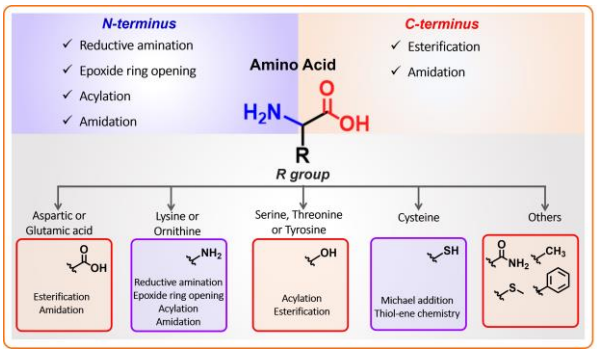


**Figure 1.** *Functional groups of amino acids and the various strategies employed for the synthesis of amino acid-based monomers.*

breakthrough in the development of amino acid-based polymers was achieved by Curtius and coworkers in 1921, through the synthesis of polypeptides using ring-opening polymerization of *α*-amino acid *N*-carboxyanhydrides (NCAs).[9] This invention has offered a promising pathway for the development of bio-inspired materials through the incorporation of natural amino acids into polymeric architectures. Since the initial discovery, various polymeric architectures, such as homopolymers, random and block copolymers, hyperbranched polymers, and others incorporating natural amino acid moieties, have emerged as promising smart materials (Figure 2A,B).[10] The design and application of these amino acid-derived polymers have become a significant focus across materials science, chemistry, and biology due to their unique and versatile properties.[11]

Sanda and Endo made significant contributions to the field by systematically classifying amino acid-functionalized polymers into two distinct categories: (i) incorporating amino acid residues within the polymer backbone, and (ii) bearing amino acid functional groups as pendant side chains.[12,13] This structural integration imparts a broad spectrum of desirable properties, including tunable amphiphilicity,[14] intrinsic chirality,[15] organocatalytic activity,[16] biocompatibility,[17] enhanced aqueous solubility,[18] and the ability to form complex self-assembled hierarchical architectures.[19] Additionally, a wide variety of polymeric nanostructures, including vesicles, micelles, nanogels, nanorods, nanofibers, etc., can be fabricated from these amino acid-containing polymers by precisely controlling the conditions governing self-assembly of polymers.[20,21] The functional properties of these nanostructures, such as size, shape, composition, surface charge, stability, porosity, and mechanical strength, can also be readily tailored to meet the specific requirements of targeted applications.[22,23] In this regard, a diverse range of amino acid-derived polymeric nanostructures has demonstrated significant potential across various biomedical applications, including antimicrobial therapies,[24] cellular interactions,[25] antifouling coatings,[26] drug delivery,[27] wound healing,[28] and tissue engineering[29] applications. O'Reilly and colleagues explored the synthesis of functional polymers incorporating amino acid moieties using controlled radical polymerization (CRP) techniques.[30] In parallel, Mori and Endo provided a comprehensive review on the fabrication of amino acid-based thermo- and pH-responsive block copolymers *via* reversible addition-fragmentation chain transfer (RAFT) polymerization, highlighting their self-assembly behavior, tunable chiroptical properties, and potential applications in catalysis and optoelectronics.[31] Our group summarized pH-responsive, side-chain amino acid-containing polymers and their potential applications.[32] Later on, a few updated reviews were also published in the area of side-chain amino acid-containing polymers.[13,33] Although a number of review articles have been published in this field,[5,34] the fundamental importance of amino acid-containing polymers warrants continued attention.

This review highlights recent advances (2015-present) and emerging trends in the design, synthesis, and biomedical applications of amino acid-containing polymers. At first, the key synthetic strategies and fundamental properties of amino acid-functionalized polymers are outlined, followed by a discussion of recent progress in their design and self-assembly. Special attention is given to their therapeutic potential in biomedical contexts. While a comprehensive exploration of this vast area of research is beyond the scope of a single review, we aim to provide a focused overview of current advancements and crucial developments in amino acid-based polymer research. Finally, we conclude with a discussion on future perspectives, emphasizing emerging directions in the design of novel amino acid-derived polymers for further advancement in the field.

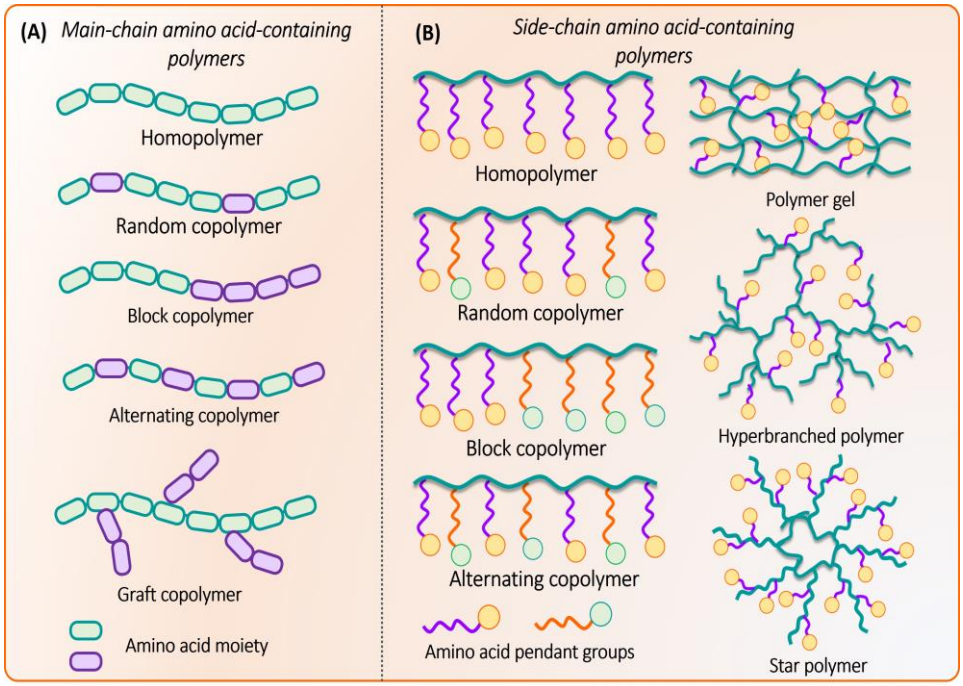


**Figure 2.** *Schematic representation of various architectures of (A) main-chain amino acid-containing and (B) side-chain amino acid-containing polymers.*

## 2. Synthesis of amino acid-containing polymers

The design of polymers from amino acids holds significant promise in bridging the gap between traditional synthetic materials and the complex functionality of natural biopolymers. Amino acids possess three primary functional groups: the amino group (-$NH_2$), the carboxyl group (-COOH), and a variable side chain (-*R* group), each offering unique chemical reactivity.[11] These unique functionalities enable the rational design and tailored synthesis of amino acid-based functional materials with broad application potentials. Since the discovery of amino acid-containing polymers, the incorporation of these amino acids into the polymer main chains has attracted considerable attention due to their intrinsic chemical versatility and biodegradability (Figure 3A).[35] A variety of synthetic strategies have been employed to construct these main chain amino acid-containing polymers, including conventional polycondensation, interfacial and solvent-free thermal polycondensation, and ring-opening polymerization (ROP) of *N*-carboxyanhydrides (NCA) and *O*-carboxyanhydrides (OCA).[34] Among these, solution-phase polycondensation has proven particularly effective for synthesizing poly(ester amide)s, poly(ether ester amide)s, and poly(ester urethane urea)s.[6] Meanwhile, polypeptides and polyesters are more commonly produced *via* ROP of NCAs and OCAs, offering precise control over molecular architecture and composition.[36]

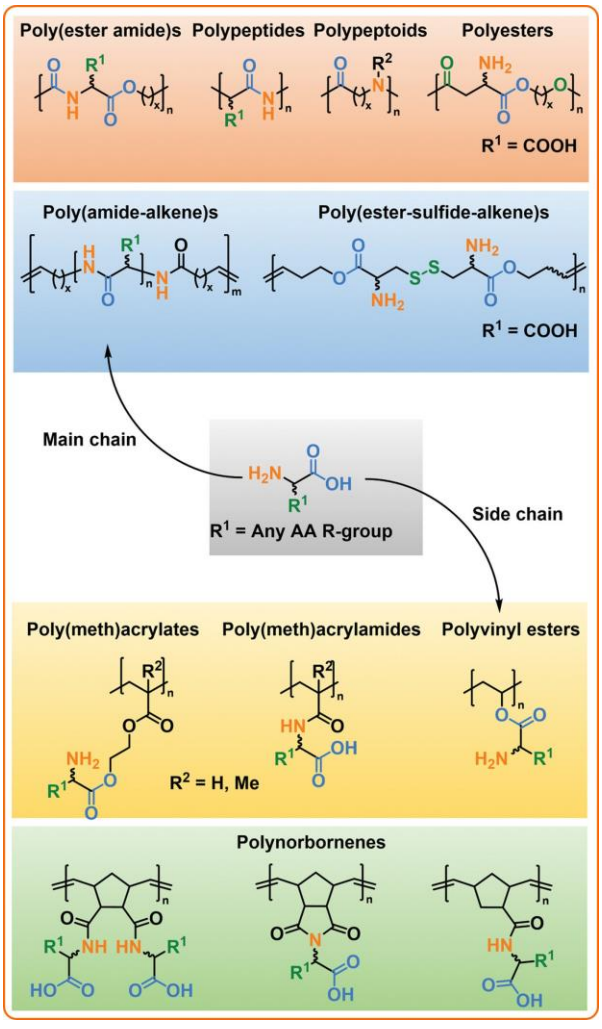


**Figure 3.** *Schematic illustration of amino acid-derived polymer synthesis, showcasing functionalization at the (A) main chain polymer backbone and (B) side-chain pendants. Adapted with permission from ref 8. Copyright (2021) Wiley-VCH GmbH.*

In recent years, polymers functionalized with side-chain amino acid moieties have emerged as highly promising candidates for a wide range of biomedical applications (Figure 3B). In the synthesis of side-chain amino acid pendant polymers, the polymerizable group can be strategically introduced at the *N*-terminus, *C*-terminus, or, in some cases, at the side-chain (-*R* group) functionalities such as -SH or -OH. Monomers modified at the *N*-terminus retain the carboxylic acid (-COOH) and side-chain -*R* group functionalities in the final polymer, whereas *C*-terminus modifications preserve the amino (-$NH_2$) group and side-chain -*R* group functionalities along the side chain. This site-specific functionalization offers precise control over the polymer architecture and functional group presentation, which is critical for tailoring material properties for biomedical applications. In the context of biomimetic polymer design, the preservation of the -*R* group is particularly critical, as it plays a vital role in dictating protein-like folding, molecular assembly, and biological function.[37] In this context, early work by Kulkarni and Morawetz laid the foundation for synthesizing poly(methacryloyl-L-alanine) and poly(methacryloyl-L-glutamic acid) from *N*-terminus-modified monomers using the conventional free radical polymerization (FRP) technique.[38] Conversely, the first report on the synthesis of *C*-terminus-functionalized monomers was presented by Sun and Gao, employing esterification reactions between 2-hydroxyethyl methacrylate (HEMA) and various protected amino acids, including phenylalanine, glycine, alanine, valine, and lysine *via* both atom transfer radical polymerization (ATRP) and FRP.[39] Later on, nitroxide-mediated polymerization (NMP) and RAFT polymerization have also been extensively used to prepare these types of polymers.[40] Our research group has made significant contributions to the development of diverse amino acid-derived polymers using RAFT polymerization, specifically through the synthesis of *C*-terminus-modified monomers, enabling the incorporation of a broad range of functional side chains into the polymer backbone.[32] The following section provides a brief overview of the structural features of amino acid-containing polymers.

## 3. Characteristics of amino acid-containing polymers

Amino acids are capable of adopting a zwitterionic structure across a broad pH range, contributing to their unique physicochemical properties.[41] However, when incorporated into the polymer backbone *via* condensation reactions to form poly(amino acids), this zwitterionic character is typically lost due to amide bond formation.[42] In contrast, functionalization at the *N*- or *C*-terminus of amino acids, followed by their incorporation into polymer side chains, enables the preservation of their inherent ionic character, yielding cationic or anionic functionalities depending on the site of modification.[15] The free -COOH and -$NH_2$ groups present in polymer side chains exhibit pH-responsive behavior, undergoing protonation or deprotonation depending on the surrounding aqueous environment.[43,44] Protonation of -$NH_2$ groups, in particular, results in the formation of cationic polymers, which are valuable for a variety of applications due to their charge-responsive behavior. These functional groups also serve as versatile reactive sites for post-polymerization modifications, enabling the introduction of tailored functionalities.[45]

Incorporating amino acid residues as pendant side chains imparts stimuli-responsive properties, such as sensitivity to temperature and ionic strength, expanding their utility in applications ranging from polyelectrolytes to chiral recognition systems and bioactive compounds.[46] Additionally, the side-chain (-*R* group) of amino acids provides a functional handle for chemical modification. For instance, -SH group of cysteine enables efficient functionalization *via* thiol-ene click or thiol-Michael addition,[47] facilitating the synthesis of zwitterionic

monomers with free *α*-amino or *α*-carboxylic acid groups. These chemically modified monomers enable the rational design and synthesis of advanced zwitterionic materials, offering tunable physicochemical properties suited for a wide range of applications. The following section presents a comprehensive overview of the biomedical applications of various amino acid-containing polymers reported since 2015.

## 4. Applications of amino acid-containing polymers

Owing to their exceptional properties, amino acid-containing polymers have emerged as advanced functional biomaterials, increasingly replacing traditional materials such as metals, ceramics, and conventional composites in various technological applications. In recent years, both their molecular forms and self-assembled nanostructures have been widely explored in diverse fields including drug delivery, gene transport, tissue engineering, biosensing, metal ion removal for water purification, and aspects of food packaging. However, in this review, we focus specifically on their biomedical applications.[48] We have discussed this under two main sections.

### 4.1. Biomedical applications of main-chain amino acid-containing polymers

Main-chain amino acid-containing polymers have garnered significant interest in biomedicine due to their inherent biocompatibility, biodegradability, and structural similarity to natural proteins. These polymers serve as promising platforms for a variety of biomedical applications, including temperature sensing, antimicrobial treatments, and tissue engineering scaffolds. Zhu and colleagues synthesized poly(L-cysteine)s containing methylthio side chains (PMTLCs) through ROP for potential use in temperature sensing applications (Figure 4A).[49] The thioether bonds in PMTLC were oxidized using hydrogen peroxide, resulting in the formation of water-soluble $PMTLC^{OX}$. Subsequently, the methylthio groups were methylated with methyl iodide, followed by an ion-exchange process to produce sulfonium-containing polypeptides (PPLC-DMS-X, where X = I or $BF_4$). These PPLC-DMS-X polymers exhibited upper critical solution temperature (UCST) behavior as well as thermo- and oxidation-responsive characteristics in aqueous environments. Both PMTLC and PPLC-DMS-X displayed a structural transition from *β*-sheet to *α*-helix upon oxidation. Furthermore, the cationic variant PPLC-DMS-I showed strong interactions with the anionic dye methyl orange (MO), resulting in a clear linear relationship between solution absorbance and temperature, highlighting its potential as a temperature sensor. In terms of biocompatibility, sulfonium-functionalized polypeptides (PPLC-DMS-I, PPLC-DMS-$BF_4$, and PPLCOX-DMS-$BF_4$) exhibited low cytotoxicity toward RAW 246.7 cells, maintaining over 75% cell viability within a concentration range of 0.02-0.2 mg/mL. In another report, Xiong and coworkers developed an antimicrobial polypeptide by incorporating anionic phosphorylated tyrosine residues into a cationic polypeptide backbone (Figure 4B).[50] They synthesized random copolypeptides, namely poly(*γ*-6-(*N*,*N*-dimethyl-*N*-octylamino)hexyl-L-glutamate)-*r*-(L-tyrosine) (abbreviated as PHOT), through the ROP of *γ*-(6-chlorohexyl)-L-glutamate *N*-carboxyanhydride (NCA) and L-tyrosine NCA. Two variants, PHOT-1 and PHOT-2, were prepared using 20 mol% and 10 mol% of L-tyrosine NCA, respectively. The resulting copolymers were then aminated using *N*,*N*-dimethyloctylamine. Phosphorylated versions of these copolymers, referred to as PHOPT, were obtained by modifying the phenolic groups of tyrosine with phosphate

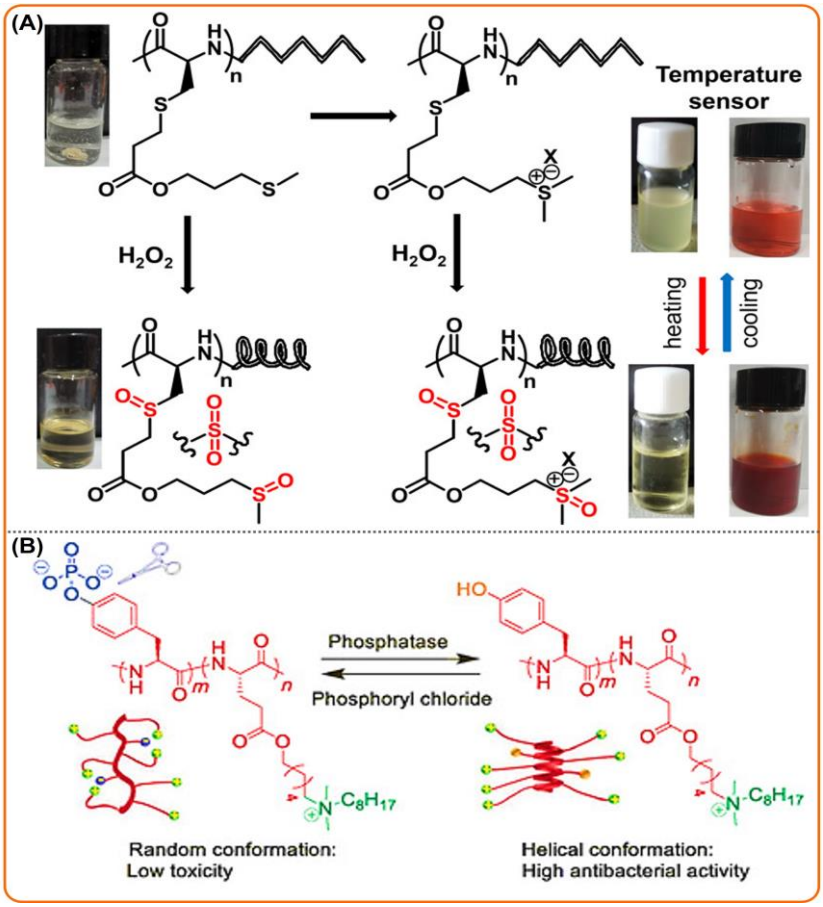


**Figure 4.** *(A) Representation of poly(L-cysteine) containing methylthio side-chain-based (PMTLCs) polymer for potential use in temperature sensing applications. Adapted with permission from ref 49. Copyright (2021) American Chemical Society. (B) Synthesis of antimicrobial polypeptide by incorporating anionic phosphorylated tyrosine residues into a cationic polypeptide backbone. Adapted with permission from ref 50. Copyright (2017) Wiley-VCH GmbH.*

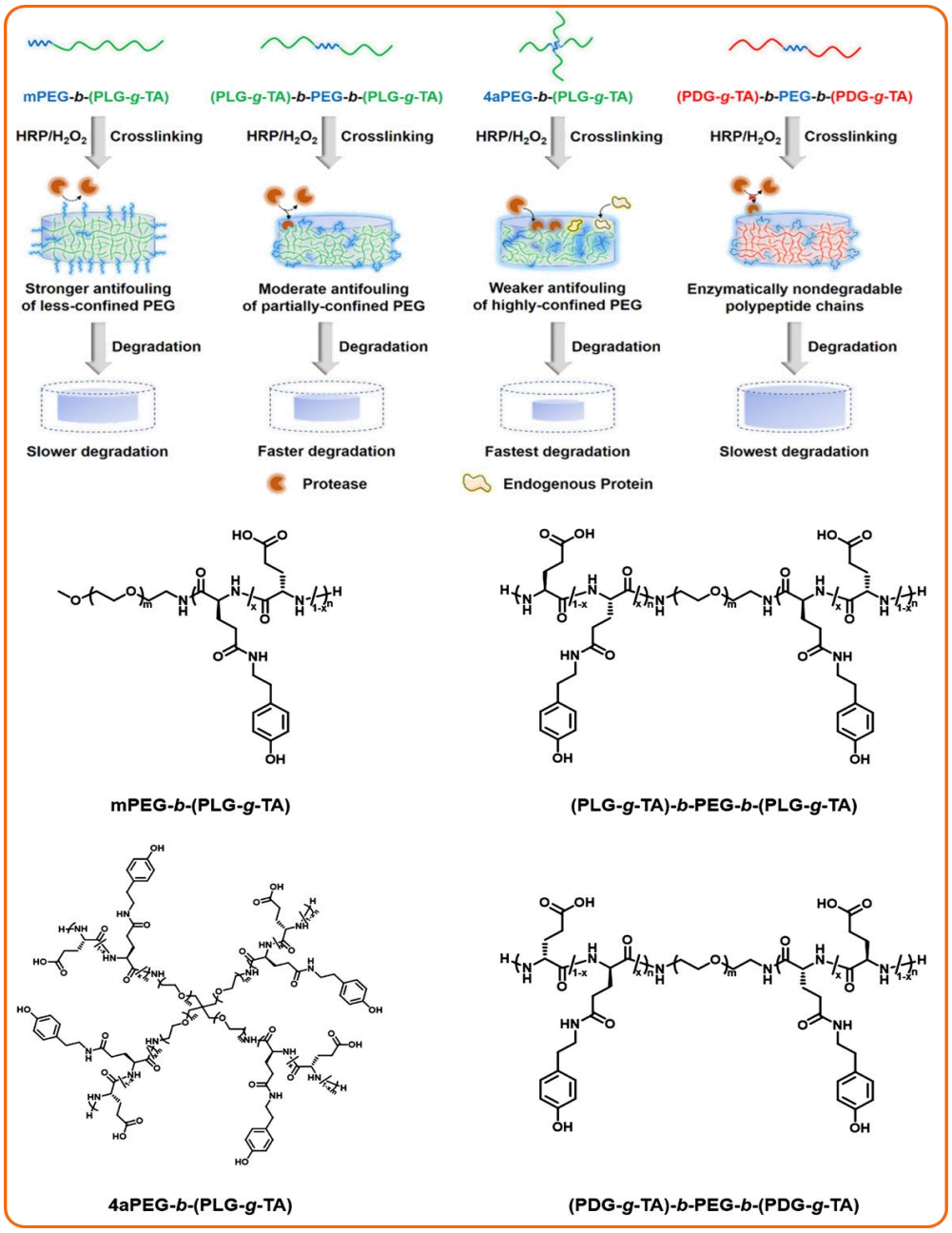


**Figure 5.** *Schematic representation of hydrogels based on poly(ethylene glycol)-block-poly(glutamic acid) copolymers, each differing in polypeptide segment topology. Adapted with permission from ref 51. Copyright (2022) American Chemical Society.*

groups. Notably, PHOPT-2, which lacks a helical structure in its phosphorylated state, can be activated by bacterial phosphatase. This enzymatic dephosphorylation restored the helical conformation, enabling effective bacterial killing while exhibiting minimal toxicity toward normal mammalian cells. Li *et al.* engineered a series of four distinct hydrogels based on poly(ethylene glycol)-*block*-poly(glutamic acid) copolymers, each differing in polypeptide segment topology and residue chirality (Figure 5).[51] These copolymers were functionalized with tyramine moieties to enable enzymatic cross-linking and hydrogel formation. The degradation behavior of both the copolymers and the resulting hydrogels was systematically assessed *in vitro* using L929 mouse fibroblast cells. Remarkably, materials incorporating D-glutamic acid exhibited substantially slower degradation rates compared to their L-glutamic acid counterparts. Furthermore, the architectural configuration of the copolymers significantly influenced the degradation kinetics of the poly(L-glutamic acid)-based hydrogels. *In vivo* evaluations using a Sprague-Dawley (SD) rat model further demonstrated that both the stereochemistry and topology of the polypeptide blocks played critical roles in modulating the biodegradability of hydrogels and host tissue response.

### 4.2. Biomedical applications of side-chain amino acid-containing polymers

Side-chain amino acid-containing polymers have emerged as versatile materials in the biomedical field due to their tunable functionality, self-assembly behavior, and excellent biocompatibility. Functional amino acid side chains enable these polymers to respond to physiological stimuli and interact with biological targets, supporting their use in antimicrobial applications, drug delivery, biosensing, inhibition of protein misfolding, and tissue engineering.

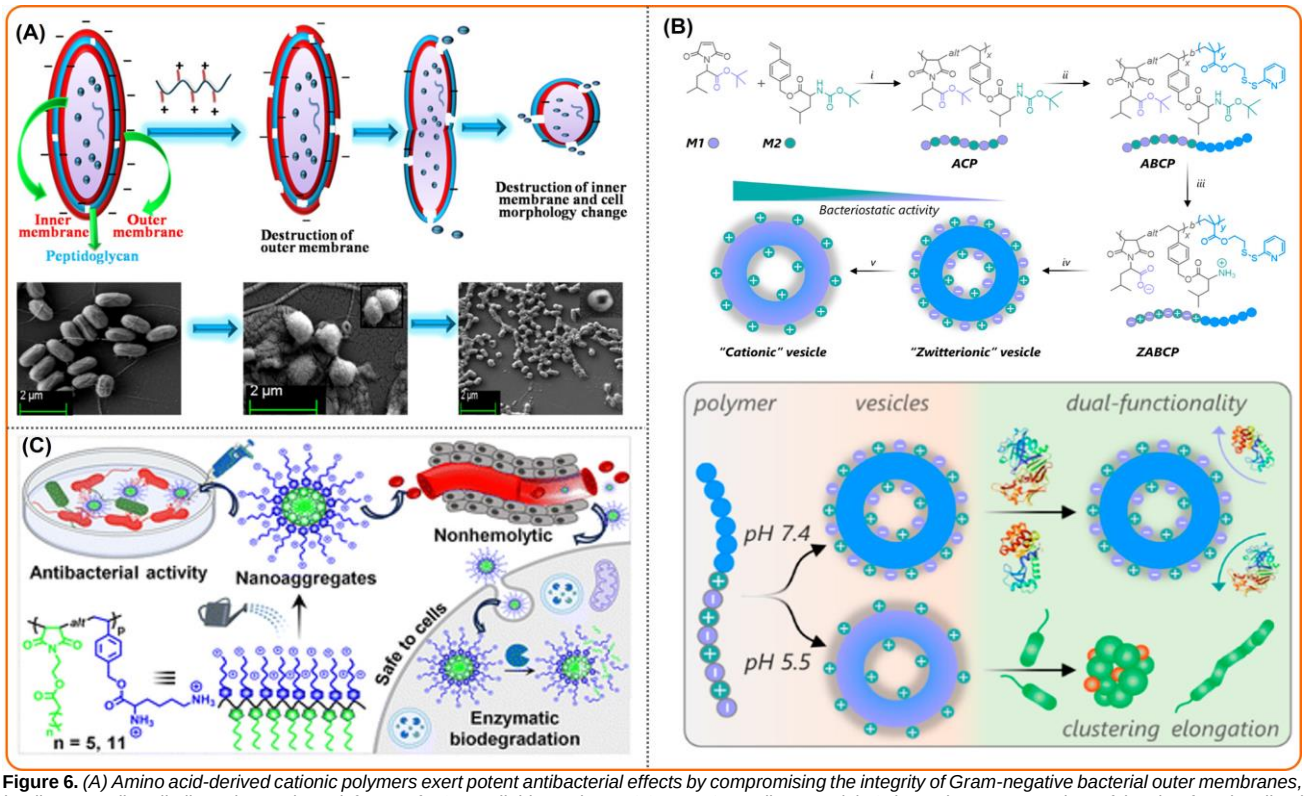


**Figure 6.** *(A) Amino acid-derived cationic polymers exert potent antibacterial effects by compromising the integrity of Gram-negative bacterial outer membranes, leading to cell wall disruption. Adapted from ref 52. Available under a CC-BY-NC-ND license. (B) Schematic representation of leucine-functionalized polyzwitterionic copolymer and the antibacterial activity. Adapted with permission from ref 53. Copyright (2024) American Chemical Society. (C) Schematic representation of side chain lysine and fatty acid pendants alternating copolymer, self-assembly, antibacterial activity, and enzymatic degradation. Adapted with permission from ref 54. Copyright (2024) Royal Society of Chemistry.*

This section highlights selected studies in the field of antimicrobial polymers, showcasing key advancements and representative examples. Mukherjee *et al.* developed a series of side-chain amino acid pendant polymers incorporating alanine, leucine, and phenylalanine moieties.[52] Among these, the polymer featuring a cationic leucine side chain demonstrated notable antibacterial activity, showing greater efficacy against *Escherichia coli* than against *Bacillus subtilis*. This differential activity arises from structural differences in bacterial cell walls, with the more anionic and hydrophilic surface of Gram-negative bacteria enabling stronger electrostatic interactions with cationic polymers, enhancing antibacterial efficacy (Figure 6A). Building upon this work, Banerjee and colleagues designed a leucine-functionalized polyzwitterionic polymer featuring alternately arranged cationic amine and anionic carboxylate groups to investigate the antimicrobial properties (Figure 6B).[53] The polymer self-assembled into bilayer vesicles with a zwitterionic surface at physiological pH (7.4), exhibiting pH-dependent surface charge transitions. At acidic pH (5.5), mimicking infection sites, the vesicles showed strong bacteriostatic activity and induced bacterial clumping, elongation, and membrane disruption, unlike the minimal effects observed at neutral pH. Ghosh *et al.* engineered an alternating copolymer incorporating lysine and fatty acid side chains, precisely tuned to achieve a balanced hydrophobic-hydrophilic profile (Figure 6C).[54] This polymer exhibited potent antibacterial activity against both *B. subtilis* and *E. coli*. Beyond its potent antimicrobial activity, the copolymer exhibited dual responsiveness to enzymatic degradation and pH fluctuations, underscoring its promise for targeted, stimuli-responsive therapeutic applications.

Significant progress has also been made in employing side-chain amino acid-containing polymers for drug delivery in cancer therapy. Kumar and coworkers developed pH-responsive self-assembled block copolymers based on

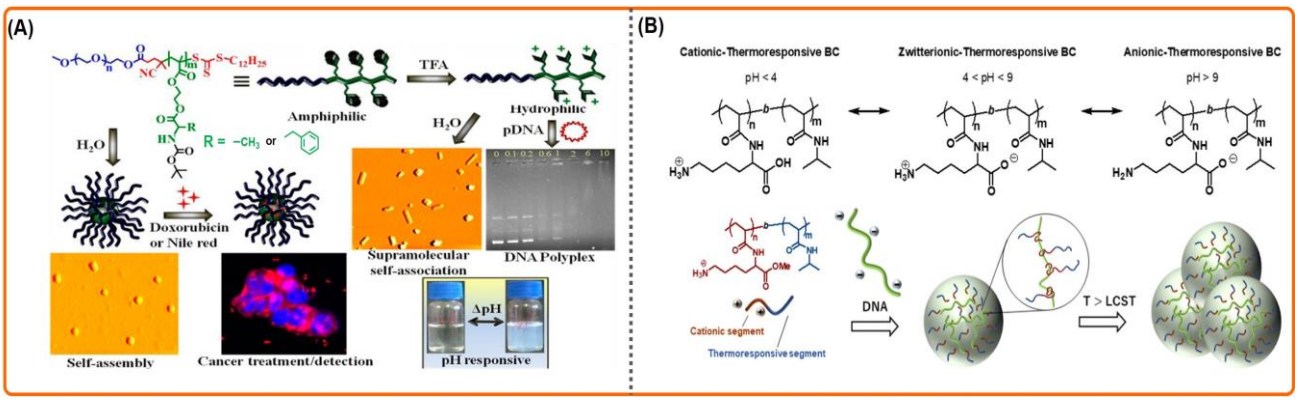


**Figure 7.** *(A) Schematic illustration of RAFT-mediated synthesis of amino acid-functionalized block copolymers and their subsequent application in DNA complexation. Adapted with permission from ref 55. Copyright (2013) American Chemical Society. (B) Synthesis, assembled structures, and DNA complexation of thermoresponsive lysine-based zwitterionic and cationic block copolymers. Adapted with permission from ref 58. Copyright (2019) American Chemical Societv.*

phenylalanine/alanine side-chain amino acids for applications in drug delivery and gene transfer (Figure 7A).[55] These polymers were capable of forming polyplex complexes with plasmid DNA. Furthermore, the self-assembled structures effectively facilitated the delivery of doxorubicin (DOX) drug to MCF-7 breast cancer cells. Li *et al.* developed a novel class of cationic poly(*ω*-aminohexyl methacrylamide)s, co-modified with L-arginine and L-histidine, capable of forming nanoscale polyplexes with plasmid DNA.[56] Experimental results highlighted that an optimized ratio of L-arginine to L-histidine is crucial for minimizing cytotoxicity while significantly enhancing cellular uptake and gene transfection efficiency. In a related study, Liu and colleagues developed a pH-responsive zwitterionic polypeptide as a promising platform for anti-tumor drug delivery.[57] By conjugating a lysine-based zwitterionic polypeptide with the chemotherapeutic agent DOX, they engineered a system capable of self-assembling into nanoparticles in aqueous environments, exhibiting clear pH-responsive behavior. The zwitterionic lysine side chains impart hydrophilicity and charge balance to the polypeptide, significantly enhancing its resistance to nonspecific protein adsorption. This anti-fouling characteristic, combined with efficient drug release under acidic conditions, superior biocompatibility, and potent anticancer efficacy, underscores its potential as an effective and intelligent drug delivery platform.

Recently, a series of lysine-based block copolymers were synthesized *via* RAFT polymerization, incorporating a thermoresponsive PNIPAM segment and a second block bearing anionic, zwitterionic, or cationic lysine side chains (Figure 7B).[58] The cationic variant effectively formed DNA polyplexes through electrostatic interactions, displaying temperature- and salt-dependent aggregation. In contrast, the zwitterionic polymer showed no DNA binding but exhibited excellent cell penetration with low cytotoxicity. These multi stimuli-responsive copolymers hold strong potential for biomedical applications and the development of smart biomaterial surfaces. Datta *et al.* developed a biocompatible block copolymer incorporating capric acid and tryptophan, where the hydrophobic fatty acid imparts water resistance and the amino acid provides hydrophilicity.[59] This amphiphilic structure enables efficient DOX encapsulation and pH-responsive release at tumor sites, while the tryptophan moiety also facilitates DNA binding and sensing.

Side-chain amino acid-functionalized polymers have also been reported to effectively inhibit protein misfolding, offering promising avenues for therapeutic intervention in protein aggregation-related disorders. Amyloid fibril formation from protein misfolding is implicated in various neurodegenerative diseases. Although arginine and proline can inhibit fibrillation, the effectiveness of proline at only high concentrations limits its biological applicability. To tackle this challenge, our group recently developed side-chain proline-based polymers that exhibited remarkable inhibition of *in vitro* insulin aggregation (Figure 8A).[60] The proposed mechanism suggests that electrostatic repulsion between similarly charged proline-based polymers and insulin molecules limits their interaction during the nucleation phase, thereby failing to significantly extend the lag phase of fibril formation. However, during the growth phase, these polymers are anticipated to bind to the ends of developing fibrils, effectively capping them and inhibiting further elongation of the amyloid structures. Building on this, Bera *et al.* investigated the influence of amino acid side chain polymer-coated silver nanoparticles on insulin fibrillation (Figure 8B).[61] Among the three tested copolymers, comprising poly(ethylene glycol) methyl ether and amino acid side chains (alanine, leucine, and phenylalanine), the phenylalanine-based polymer-coated nanoparticles demonstrated the most significant effect, achieving up to 96% inhibition of insulin aggregation. In a related study, Nayak and colleagues investigated side-chain proline-based polymers conjugated with an amyloid *β*-peptide segment as potent inhibitors of lysozyme amyloidosis (Figure 8C).[62]

Beyond their previously discussed applications, amino acid-containing polymers have also been explored for their ability to regulate actin dynamics, a critical process governing cytoskeletal movement. Since actin filament remodelling is essential for key cellular functions such as motility, division, and intracellular transport, these polymers hold significant promise in influencing cell behavior at the molecular level. Maiti

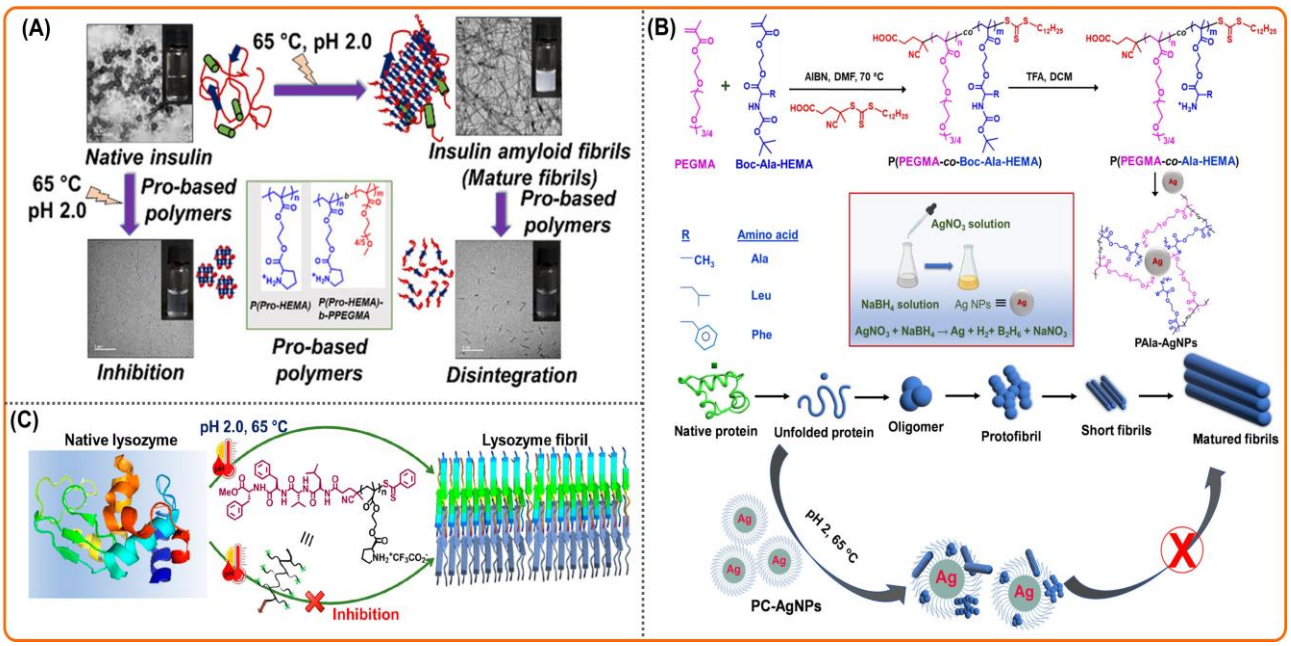


**Figure 8.** *(A) Illustration of side-chain proline-based polymers and inhibition of in vitro insulin aggregation. Adapted with permission from ref 60. Copyright (2020) American Chemical Society. (B) Structural representation of amino acid side chain polymer-coated silver nanoparticles and their effect on insulin fibrillation. Adapted with permission from ref 61. Copyright (2023) American Chemical Society. (C) Schematic representation of side-chain proline-based polymers conjugated with an amyloid β-peptide segment for the inhibition of lysozyme amyloidosis. Adapted with permission from ref 62. Copyright (2024) American Chemical Society.*

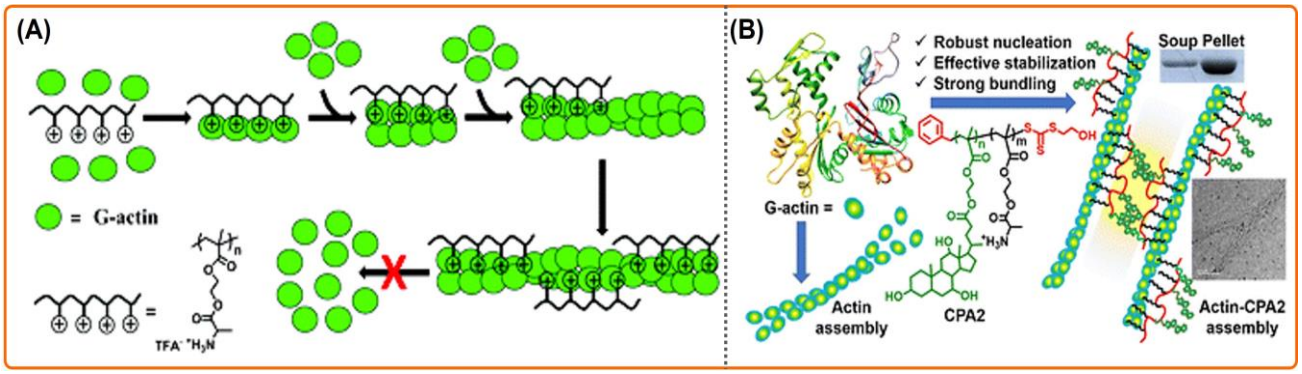


**Figure 9.** *(A) Side-chain alanine-functionalized cationic polymer and its effect on actin polymerization. Adapted with permission from ref 63. Copyright (2017) Royal Society of Chemistry. (B) Side-chain amino acid-functionalized and cholic acid pendant copolymer for the study of actin nucleation dynamics. Adapted with permission from ref 64. Copyright (2022) Royal Society of Chemistry.*

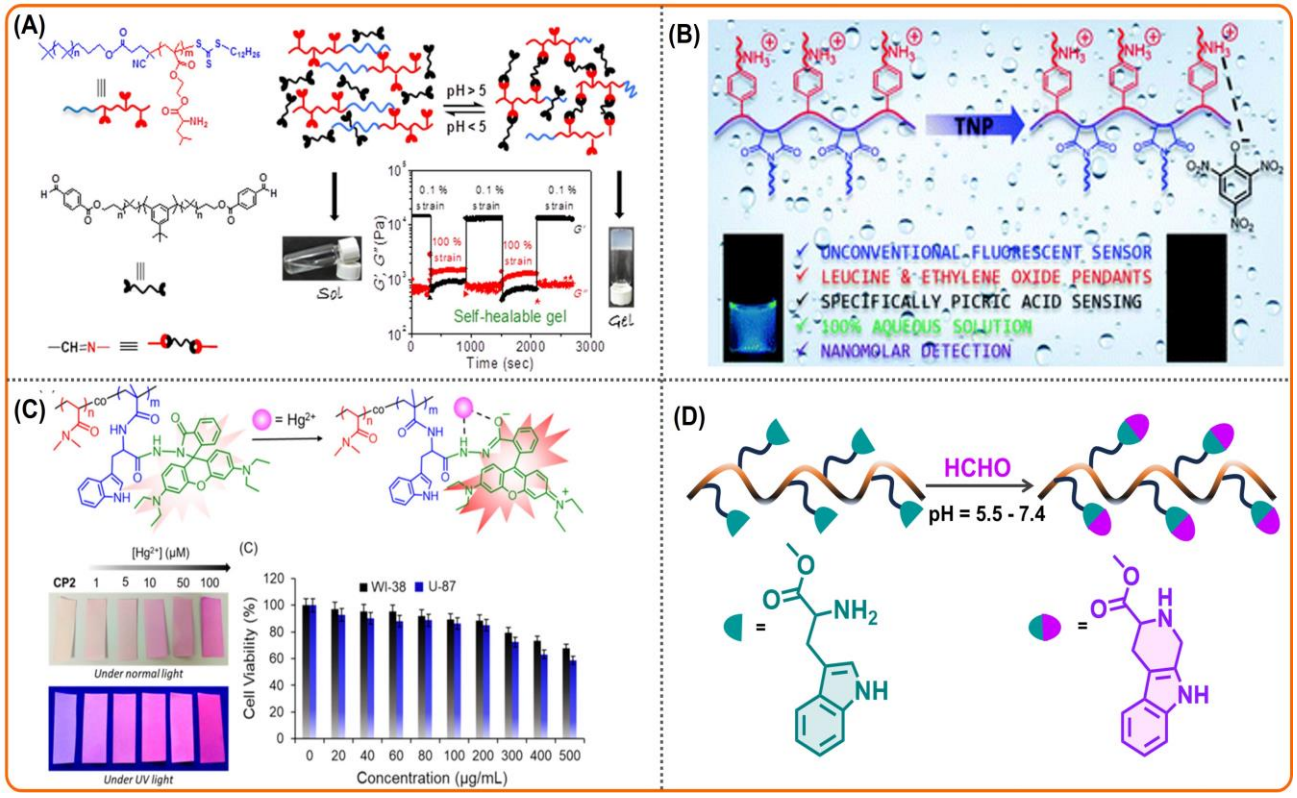


**Figure 10.** *(A) Diblock copolymer of PIB bearing leucine-derived primary amine side chains and the corresponding self-healing gel. Adapted with permission from ref 67. Copyright (2015) American Chemical Society. (B) Schematic representation of leucine-conjugated water-soluble fluorescent copolymer and the detection of picric acid. Adapted with permission from ref 69. Copyright (2017) Royal Society of Chemistry. (C) Tryptophan and rhodamine functionalized water-soluble random copolymer for fluorometric detection of $Hg^{2+}$ ions. Adapted with permission from ref 70. Copyright (2020) American Chemical Society. (D) Tryptophan side-chain pendant water-soluble copolymer for the detection of formaldehyde.*

*et al.* reported the effect of a side-chain alanine-functionalized cationic polymer on actin polymerization (Figure 9A).[63] They proposed that the polymer interacts with multiple G-actin monomers, promoting the formation of a stable actin nucleus, which acts as a template to enable the elongation of filamentous actin through continued monomer addition. In another report, the effect of amino acid residues (Ala, Phe, and Leu), and a cholate moiety at the polymer end chain and in side chains were monitored in modulating actin nucleation dynamics (Figure 9B).[64] Among the various amino acids, Ala showed the highest activity. The side-chain cholate-conjugated Ala-based polycationic amphiphiles provided better control over actin dynamics compared to chain-end cholate-functionalized copolymers. Thus, the ability of these polymers to modulate actin dynamics highlighted their potential as a selective and powerful tool for actin-targeted biomedical applications.

In wound healing, highly biocompatible dressings that maintain a moist environment are essential. Amino acid–based polymers are especially promising due to their biocompatibility and dual hydrophilic–hydrophobic functional groups, enabling effective interactions with biological tissues. For example, Park *et al.* grafted L-alanine onto chitosan using L-alanine-*N*-carboxyanhydride (Ala-NCA) *via* ROP, producing polyalanine side chains along the chitosan backbone.[65] The resulting alanine-grafted chitosan (Ala-*g*-Cts) films were then cross-linked using glutaraldehyde. The results demonstrated that Ala-*g*-Cts is a promising material for tissue regeneration and wound dressing applications. Zu and coworkers developed a peptide-functionalized hydrogel composed of methyl methacrylate lysine (Lys)-based poly(ester amide), methoxy polyethylene glycol methacrylate, and 2-aminoethyl methacrylate hydrochloride through a photo-cross-linking

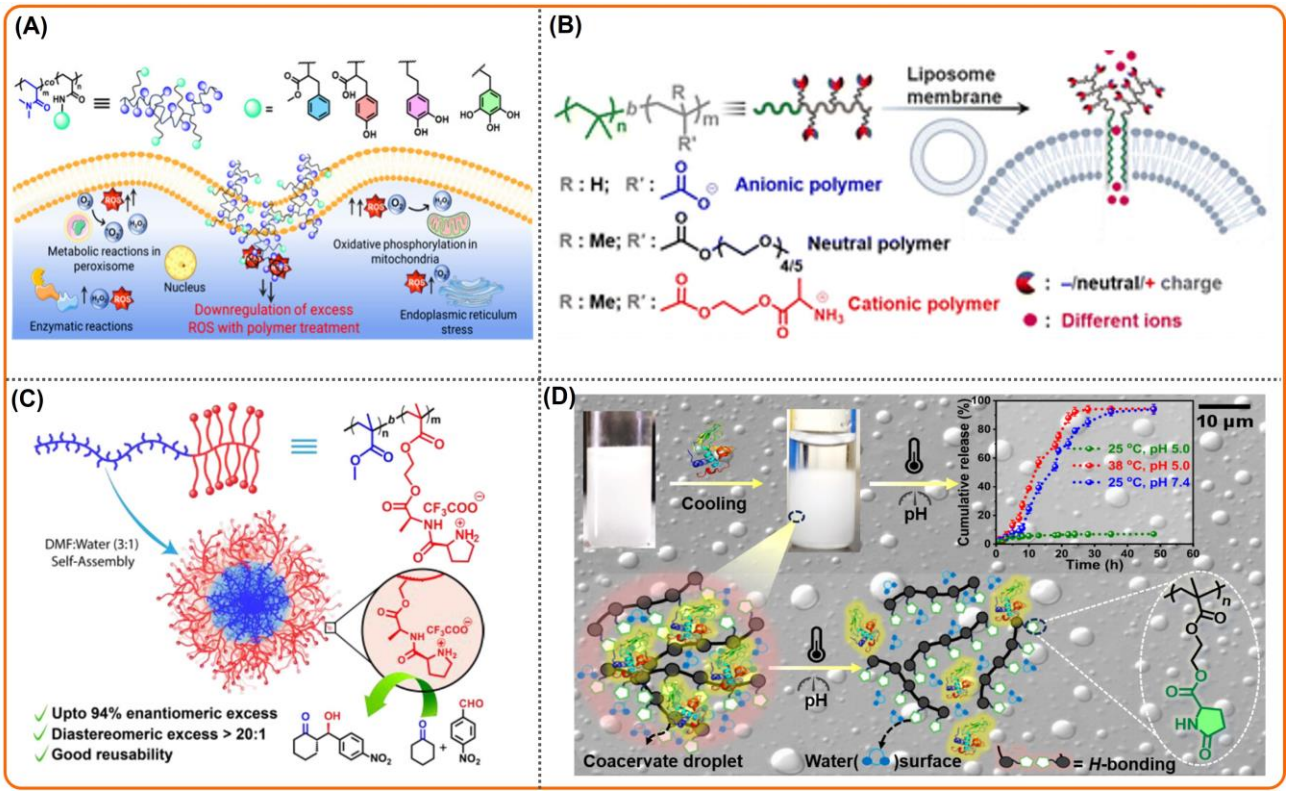


**Figure 11.** *(A) Schematic representation of amino acid and gallol side chain pendant water-soluble antioxidant copolymers. Adapted with permission from ref 73. Copyright (2024) American Chemical Society. (B) PIB-based polymers with amino acid side-chain pendants for ion transport capabilities. Adapted with permission from ref 74. Copyright (2023) Royal Society of Chemistry. (C) Side-chain L-proline-L-alanine dipeptide-functionalized block copolymer as an efficient organocatalyst for the aldol reaction. Adapted with permission from ref 76. Copyright (2024) American Chemical Society. (D) Synthesis of coacervate droplets from pyroglutamic acid-based stimuli-responsive homopolymer. Adapted with permission from ref 77. Copyright (2024) American Chemical Society.*

approach.[66] This hydrogel markedly accelerated wound healing, highlighting its potential as an effective hemostatic agent and a promising wound dressing for treating infected wounds.

In addition to their well-established biomedical roles, amino acid-based polymers have also demonstrated remarkable potential in other fields. Side-chain amino acid-containing polymers have been strategically designed for the development of stimuli-responsive soft materials.[67] Halder and coworkers reported the formation of self-healing gels using diblock copolymers of polyisobutylene (PIB) bearing leucine-derived primary amine side chains. These gels were cross-linked using a PIB-based dialdehyde crosslinker (through dynamic imine (Schiff base, -HC=N-) bond formation), enabling gelation without the need for any external stimuli (Figure 10A). Remarkably, the imine bonds exhibit reversible breaking and reformation over multiple cycles, simply by modulating the pH of the system through alternating addition of acid and base. These dynamic, self-healing gels represent a promising class of smart soft materials, with potential applications in tissue regeneration, organ repair, and pH-responsive delivery of bioactive molecules. Saha *et al.* synthesized a fluorophore-free, leucine-conjugated water-soluble fluorescent copolymer, capable of dual responsiveness to pH and temperature.[68] This smart polymer was subsequently employed for the rapid, selective, and highly sensitive detection of picric acid in a fully aqueous environment (Figure 10B).[69]

Amino acid-functionalized pendant polymers have also been extensively explored for the selective sensing and efficient removal of heavy metal ions from aqueous environments. Choudhury and coworkers reported the development of a water-soluble random copolymer derived from tryptophan, functionalized with a rhodamine moiety, enabling highly sensitive colorimetric and fluorometric detection of $Hg^{2+}$ ions in both aqueous media and live cells (Figure 10C).[70] In a related study, they synthesized a fluorescent copolymer *via* RAFT polymerization using Boc-tryptophan methacryloyloxyethyl ester and *N*,*N*-dimethylacrylamide. Following Boc deprotection and post-polymerization modification with 2-pyridinecarboxaldehyde, the resulting water-soluble copolymers, and even the hydrophobic homopolymer, demonstrated excellent sensitivity toward $Cu^{2+}$ and $Hg^{2+}$ ions in water.[71] A similar kind of tryptophan side chain pendant water soluble polymer was also used for the detection of formaldehyde (Figure 10D).[72]

The naturally occurring amino acid L-3,4-dihydroxyphenylalanine (L-DOPA), a biosynthetic precursor to dopamine, a vital neurotransmitter in the brain, has inspired the development of a series of water-soluble antioxidant copolymers to investigate their effect on mitigating cellular oxidative stress (Figure 11A).[73] Artificial ionophores facilitate selective transmembrane ion transport, an important cellular process, and disruption of this transport is linked to various diseases. In this context, Dey *et al.* investigated PIB-based polymers bearing amino acid side-chain pendants, demonstrating their ion transport capabilities across artificial membranes, thereby offering valuable insights into the design of synthetic ion channels (Figure 11B).[74] Amino acid-conjugated polymers have also been explored for their potential in organocatalysis, with the O'Reilly group being among the pioneers in advancing this field.[75] Recently, from our group, side-chain L-proline-L-alanine dipeptide-functionalized block copolymers were explored as efficient organocatalysts for the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde with high enantioselectivity at a low catalyst loading (Figure 11C).[76] Amino acid-conjugated thermoresponsive polymers have also been investigated for

the design of coacervate droplets, offering dynamic platforms for compartmentalized biochemical processes. A pyroglutamic acid-based stimuli-responsive homopolymer was developed, exhibiting UCST behavior and forming reversible micrometer-sized coacervate droplets upon cooling (Figure 11D).[77] These droplets efficiently encapsulate diverse cargoes, including small hydrophobic dyes, hydrophilic anticancer drugs, and labeled proteins, highlighting the versatility of amino acid side-chain-derived polymers for broad biomedical applications. Overall, amino acid-conjugated polymers represent a multipurpose and promising class of materials, offering versatile functionality, biocompatibility, and stimuli-responsiveness that make them highly suitable for a wide range of biomedical applications.

## 5. Conclusion and future outlook

This review highlights a comprehensive overview of recent breakthroughs in the design and synthesis of amino acid-functionalized polymers, emphasizing their promise across a range of advanced applications. Beyond their cost-effectiveness, amino acids confer a wide range of functional advantages when integrated into the polymer backbone. These include tunable optical and catalytic properties, the ability to drive self-assembly, selective interactions with biomolecules for targeted delivery, and inherent biocompatibility, making them highly valuable components in advanced polymer design. While main-chain amino acid-containing polymers hold significant importance, the emergence of side-chain amino acid-functionalized polymers has garnered growing interest in the past two decades due to their enhanced versatility and expanded functional capabilities. A key advantage of utilizing amino acid residues in the polymer side chains lies in the versatility they offer for functional group modification. This tunability provides greater structural and functional diversity compared to polymers where amino acids are incorporated into the main chain. Additionally, by carefully balancing hydrophilic and hydrophobic components within these polymers, researchers have been able to engineer a wide array of nanostructures through self-assembly. These include spherical and worm-like micelles, vesicles, and core-shell nanogels, showcasing the broad morphological potential of side-chain amino acid-based polymer systems.

In addition to their inherent ability to self-assemble into a variety of nanostructures, these polymers possess several desirable properties, such as stimuli-responsiveness, excellent aqueous solubility, high bioavailability, low cytotoxicity, that collectively make them highly attractive for desired biomedical applications. Importantly, the success of these applications depends on the intelligent molecular design of the polymers. This includes incorporating appropriate cationic charge for efficient gene delivery, achieving a fine balance between hydrophilic and hydrophobic components to regulate antimicrobial activity, engineering zwitterionic structures for antifouling functionality, and tuning hydrogel properties to support uses such as self-healing surgical dressings or scaffolds for ligament and tendon regeneration.

Amino acid–derived smart and functional polymers represent a highly promising class of biomaterials with broad applicability in biomedical fields, including drug delivery, tissue engineering, regenerative medicine, and biosensing. Their inherent structural versatility, tunable functionality, and intrinsic biocompatibility make them attractive candidates for clinical translation. Nevertheless, despite their potential, several critical challenges continue to limit their widespread adoption and must be systematically addressed through advanced material design, and innovative translational strategies. One of the most significant issues relates to biodegradability, which is a highly desirable feature for biomedical applications. However, achieving an optimal and predictable degradation profile in amino acid–based smart polymers remains a considerable challenge. Excessively rapid degradation may lead to premature loss of structural integrity, thereby compromising tissue support or sustained therapeutic release. Conversely, overly slow degradation can impede tissue regeneration, cause long-term accumulation, or interfere with normal physiological processes. Thus, striking a finely tuned balance between stability and biodegradability is essential, and requires careful control over polymer architecture, amino acid composition, crosslinking density, and environmental responsiveness. Another important consideration is biocompatibility and immunological response. While amino acid–derived polymers are generally perceived as biocompatible due to their biomimetic nature, adverse biological responses cannot be excluded. For instance, certain chemical modifications, functional groups, or degradation byproducts may elicit local inflammation, immunogenicity, or even allergic reactions. The degree of compatibility is strongly influenced by factors such as polymer composition, surface chemistry, and the dynamic interactions with surrounding tissues and cellular environments. Comprehensive evaluation of immunogenicity and toxicity, both *in vitro* and *in vivo* condition remains indispensable for ensuring their safety profile prior to clinical use. The regulatory and translational hurdles must be overcome before amino acid–based smart polymers can advance into clinical practice. Beyond demonstrating efficacy in controlled experimental settings, these materials must undergo stringent safety evaluations, long-term performance studies, and compliance with regulatory frameworks governing medical devices, biomaterials, and therapeutics. Furthermore, emerging strategies, such as the integration of computational modeling, high-throughput screening, and bioinspired design principles are expected to accelerate innovation in this field. Thus, although amino acid–derived smart polymers hold considerable promise for next-generation biomedical applications, their successful translation hinges on addressing challenges related to biodegradability, biocompatibility, regulatory compliance, and large-scale production. With continued research, innovation, and collaborative efforts, these polymers are anticipated to become pivotal components of advanced therapeutic platforms and to significantly expand their role in the future of biomedicine.

## Author Contribution Declaration

With the overall supervision of P.D., A.M. wrote the manuscript with the help of D.M. and S.S. All authors equally contributed in the editing and refinement of the final manuscript.

## Data Availability Declaration

This review neither generates nor analyzes new data, nor does it present any primary research findings or employ specialized software.

## Declaration of Conflict of Interest

The authors have no conflict of financial interest.

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