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REVIEW

Polymers Facilitating Therapeutic Efficacy and Applications for Traditional Chinese Medicine

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ABSTRACT

The active ingredients from traditional Chinese medicine (TCM) are fundamental to its therapeutic efficacy. However, their difficult detection, low solubility, poor stability, uncertain biocompatibility, and inefficient absorption rate, hinder their clinical application. Polymers have emerged as a viable solution to these issues, providing a platform for the detection, enrichment, and exertion of pharmacological effects. This review delves into the application of polymers in active ingredients from TCM, covering various aspects including molecularly imprinted polymers (MIPs), polymer micelles, polymer hydrogels, conjugated polymers, and polymer nanoparticles (NPs). These advanced systems leverage the designability, adjustable solubility, and biocompatibility of polymers to enhance the therapeutic potential of TCM. The review concludes by discussing the current challenges and prospects of using polymers in TCM. It aims to provide a comprehensive understanding of the field, highlighting the potential of polymers to revolutionize TCM practices and contribute to the modernization of TCM.

1 | Introduction

Traditional Chinese Medicine (TCM) stands as one of China's oldest and most cherished legacies, offering a wealth of medicinal knowledge and therapeutic technologies for addressing a diverse spectrum of diseases. Its efficacy in managing infectious, chronic, and complex conditions has earned increasing attention on a global scale [1, 2]. A pivotal moment in the recognition of TCM's value was the awarding of the Nobel Prize in Physiology or Medicine to Prof. Tu Youyou for her great contribution to artemisinin, marking a major landmark in the international acknowledgment of TCM's contributions to healthcare. The therapeutic advantages of TCM in disease treatment are multifaceted. Firstly, the comprehensive regulatory effect of TCM not only addresses the symptoms of the disease but also aims to restore and maintain the body's overall balance, thereby enhancing immunity and potentially reducing the risk of recurrence. Secondly, TCM employs various methods of administration, including decoctions, pills, plasters, and wines. Moreover, the composition of herbal formulas can be tailored to the individual's condition. Flexible and diverse treatment methods allow TCM to offer a personalized approach to treatment. Thirdly, derived predominantly from natural sources such as plants, animals, and minerals, TCM generally exhibits fewer toxicities compared to synthetic drugs, contributing to their safety profile.

Active ingredients from TCM refer to the pharmacologically active chemical components within these traditional preparations. Representing the material foundation for TCM's efficacy, the majority of these active ingredients (approximately 87%) are plant-derived [3]. Their significant therapeutic effects on

diseases and health benefits have made them a staple in the medical field. Despite huge advantages, several challenges still exist that limit their clinical application, including difficult detection or extraction, uncertain safety, limited water solubility, low bio-absorbability, and inadequate targeting [3–5]. Nevertheless, current research confirms that the therapeutic potency of active ingredients from TCM is largely attributed to their active functional groups, such as carboxyl, hydroxyl, phenol, and amine groups [5]. These groups are prevalent in TCM ingredients and are crucial for exerting pharmacological effects, resolving compatibility issues, facilitating synergistic interactions among multiple components, and enabling biological targeting.

Polymers, as macromolecules composed of repeating monomer units linked by chemical bonds, can be either natural or synthetic [6, 7]. Their wide array of sources, tunable properties, good biocompatibility, and flexible processing make them particularly attractive in biomedical applications, such as pharmaceutical delivery [8–10]. In the context of TCM, polymers have been employed to enhance the performance of active ingredients by serving as detectors [11, 12], carriers [13, 14], sustained-release systems [15, 16], or modified ingredients [17, 18]. This approach aims to improve the efficiency, solubility, stability, and bioavailability of the active ingredients, as well as to achieve targeted drug delivery. The development of polymers for TCM applications has led to the creation of various forms, including molecularly imprinted polymers (MIPs), polymer nanoparticles (NPs), polymer micelles, polymer hydrogels, and conjugated polymers. These polymer-based formulations can address some of the limitations of traditional TCM formulations, while also introducing new design opportunities and degradability properties. The employment of polymers in TCM holds the promise of revolutionizing the field by offering more effective methods, thereby improving patient outcomes and expanding the therapeutic applications of TCM.

This review intends to explore the as-developed and potential applications of polymers in the active ingredients from TCM (see Figure 1) and address the challenges associated with polymer-based strategies, thereby enhancing their therapeutic application in modern medicine and promoting the further development of TCM.

2 | Active Ingredients FROM TCM

The complexity of TCM from its diverse array of active ingredients, each endowed with a distinct chemical composition and pharmacological profile (see Figure 2). A comprehensive exploration of these active constituents is indispensable for elucidating the intricate pharmacodynamic mechanisms underlying TCM's therapeutic efficacy. Such in-depth research is instrumental in optimizing drug design, guiding synthetic strategies, and facilitating the modification of TCM formulations to enhance their stability.

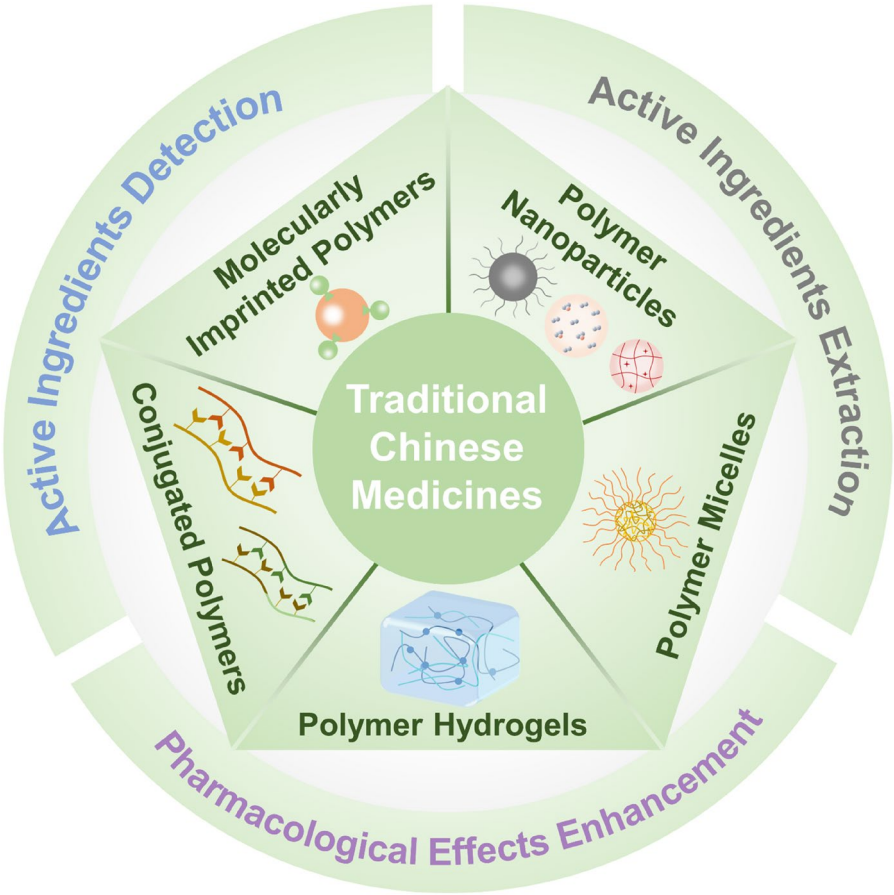

FIGURE 1 | The applications of polymers for the active ingredients from TCM.

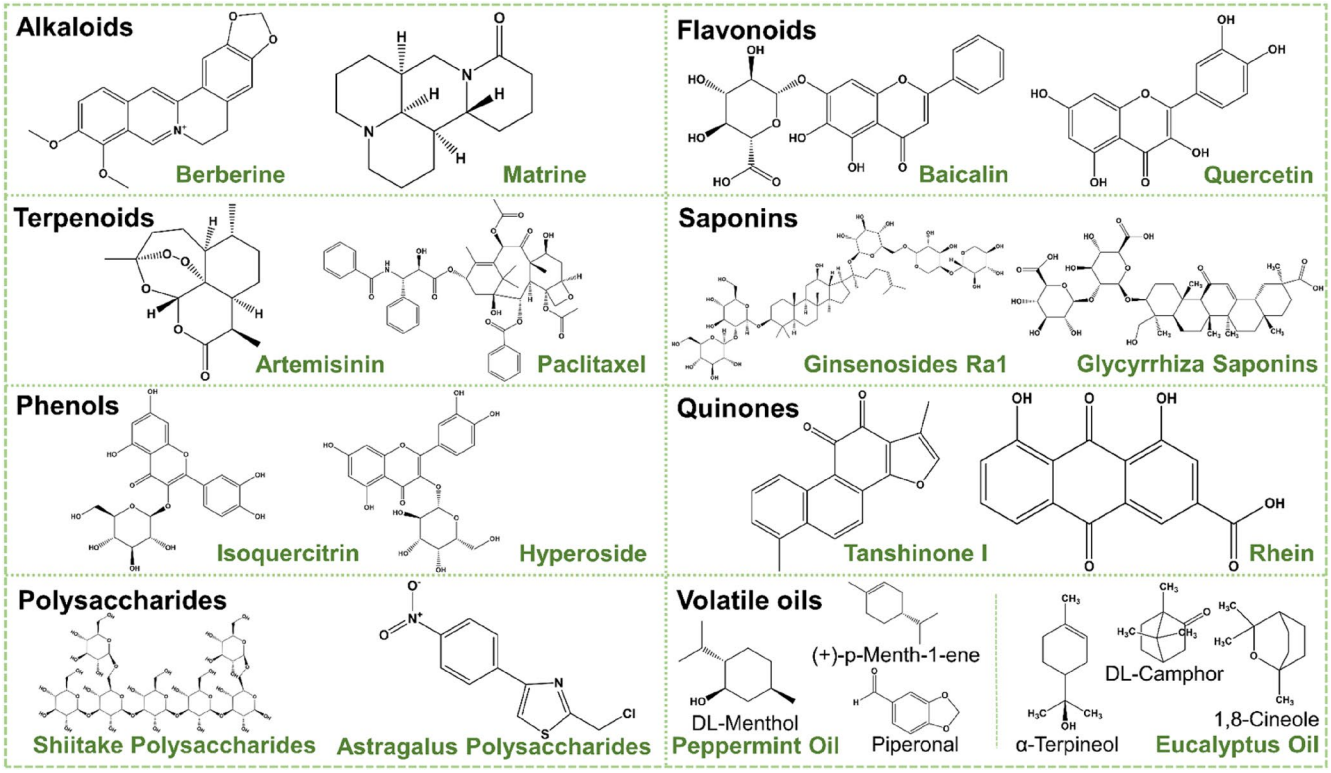

FIGURE 2 | Molecular structure of some active ingredients from TCM, including alkaloids berberine and matrine, flavonoids baicalin and quercetin, terpenoids artemisinin and paclitaxel, saponins ginsenosides Ra1 and glycyrrhiza saponins, phenols isoquercitrin and hyperoside, quinones tanshinone I and rhein, polysaccharides shiitake polysaccharides and astragalus polysaccharides, volatile oils peppermint oil and eucalyptus oil.

2.1 | Alkaloids

Alkaloids, characterized by their nitrogen-containing heterocyclic structures, exhibit a wide array of biological activities and play a pivotal role in numerous TCM practices [19]. Alkaloids are primarily found in higher plants, particularly in families such as Ranunculaceae, Papaveraceae, Apocynaceae, and Solanaceae, while their occurrence in the animal kingdom is rare. Depending on their chemical structures, alkaloids can be classified into multiple subgroups, including pyridines, indoles, quinolines, and isoquinolines, among others [20]. Prominent examples of alkaloids like berberine, matrine, monocrotaline, and ephedrine, each of which has distinct pharmacological properties. The complex ring structures of alkaloids often incorporate nitrogen atoms, which contribute to their alkaline properties and the ability to form salts with acids. Moreover, due to the nitrogen-containing heterocycles interacting with the active sites of receptors and enzymes, these compounds exhibit significant physiological activities. The pharmacological effects of alkaloids are diverse, including analgesic, antibacterial, antitumor, central nervous system, and immune system regulatory properties [21, 22].

2.2 | Flavonoids

Flavonoids are a ubiquitous class of secondary metabolites in the plant kingdom, which include well-known compounds such as baicalin, quercetin, rutin, and puerarin [23]. The majority of flavonoids are found in the form of glycosides or aglycones in plants, with some existing in their free form. The core structure of flavonoids is a flavonoid skeleton, which consists of two benzene rings (denoted as A and B rings) connected by three carbon atoms, forming a carbon ring [24]. This carbon ring is what distinguishes flavonoids from other classes of phenolic compounds. The chemical diversity of flavonoids arises from the presence of various substituents attached to the A, B, and C rings. These substituents can include hydroxyl, methoxy, alkoxy, isopentenyloxy, and other functional groups. The presence of these auxochromic groups contributes to the characteristic yellow coloration of many flavonoids. The biological activities of flavonoids are multifaceted, encompassing a range of physiological functions and pharmacological effects. They are known for their defense against pathogens and insects, as well as antitussive, expectorant, antioxidant, anti-inflammatory, and antibacterial properties, which make flavonoids valuable components in TCM.

2.3 | Terpenoids

Terpenoids, along with their derivatives, originate from the precursor mevalonic acid. They are distinguished by the presence of incorporation units (C5 units) as the primary constituents of their molecular skeletons [25, 26]. Notable terpenoids include artemisinin, paclitaxel (PTX), and ginkgolide, which are found in a variety of organisms such as higher plants, fungi, microorganisms, insects, and marine organisms, with a particularly rich distribution in the plant kingdom. Terpenoids can be classified based on the number of isoprene units they contain, which includes monoterpenes, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes. The biological activities of terpenoids are often associated with specific structural features, such as double

bonds, ring structures, and functional groups. These substances have shown a spectrum of pharmacological effects, encompassing anti-neoplastic, anti-inflammatory, anti-malarial, anti-viral, anti-oxidative, cardio-protective, and hypoglycemic effects [27, 28].

2.4 | Saponins

Saponins comprise a class of compounds characterized by a unique structural attribute: each molecule consists of a lipophilic sapogenin and a hydrophilic sugar moiety, joined together via a glycosidic linkage [29]. This unique composition gives saponins a relatively large molecular mass, typically ranging from 700 to 2000. In TCM, saponins are found in herbs such as ginseng (ginsenosides Ra1), licorice (glycyrrhiza saponins), bupleurum (bupleurum saponins), anemarrhena (anemarrhena saponins), and wild yam (diosgenin). Saponins can be classified into two structural categories according to the aglycone (the core sapogenin) structure: triterpenoid saponins and steroidal saponins [30]. The pharmacological effects of saponins are intricately linked to the specific sugar group and the sapogenin component of their molecular structure, particularly the hydroxyl groups on the sugar molecules and the functional groups on the aglycone [31, 32]. Modern pharmacological research has revealed that many natural saponins possess a broad range of substantial pharmacological activities. Among these are anti-inflammatory, antiviral, anti-aging, hepato-protective, and therapeutic effects against cardiovascular and cerebrovascular diseases [33].

2.5 | Phenols

Phenolic substances are compounds characterized by the presence of a benzene ring to which a hydroxyl group is directly attached [34, 35]. This structural feature gives rise to compounds such as isoquercitrin, hyperoside, chlorogenic acid, quercitrin, ferulic acid (FA), epicatechin, etc. Phenolic substances are pervasive in nature, occurring in plants, animals, and microorganisms. The biological activity of phenolic substances is closely associated with the hydroxyl groups in their molecular structure, particularly the hydrogen atoms attached to these hydroxyl groups. These hydrogen atoms are capable of forming hydrogen bonds, which influence the water solubility, antioxidant activity, and interactions of the compounds with other biological molecules. Phenolic compounds are known for their free radical scavenging, anti-inflammatory, antiviral, immunomodulatory, anticoagulant, and anti-tumor effects [36, 37]. These activities have garnered increasing attention and are considered to be the primary reducing agents in TCM, where they contribute to the overall health benefits associated with TCM methodologies.

2.6 | Quinones

Quinone compounds feature quinone ring structures. These compounds are represented by substances such as tanshinone, rhein, and shikonin, which are primarily found in the plant kingdom, particularly in the roots, stems, leaves, and flowers of various plants [38]. Quinone compounds can be categorized into four structural types based on the configuration of their aromatic rings: benzoquinones, naphthoquinones, phenanthrenequinones, and anthraquinones [39]. The quinone ring is typically modified by various functional groups, including hydroxyl, methyl, and ethyl groups, which significantly influence the solubility, stability, and interactions of the compounds with other biological molecules [40]. The biological activities of quinone compounds are diverse, mainly embodied in laxative, antibacterial, hemostatic, and coronary{Citation} artery dilation effects [41].

2.7 | Polysaccharides

Polysaccharides represent the group of carbohydrates characterized by their high molecular weights, which are formed by the interlinking of numerous monosaccharide units through glycosidic bonds [42, 43]. These fundamental units, such as glucose, galactose, and arabinose, combine to form polymers with molecular weights that can span several orders of magnitude, from thousands to millions of atomic mass units. Polysaccharides are ubiquitous in the natural world and are prominently featured in various types of TCM derived from plants, animals, and fungi. Examples include the well-studied shiitake polysaccharides, astragalus polysaccharides, ginseng polysaccharides, and tuckahoe polysaccharides. The biological activities of polysaccharides are intricately linked to their molecular architecture, particularly the nature and arrangement of the monosaccharide units and the glycosidic bonds that connect them [43]. These structural elements dictate the polysaccharides' capacity to engage with and modulate biological molecules, thereby influencing their pharmacological effects. Contemporary pharmacological research has elucidated the biological activities of polysaccharides, including their capacity to modulate the immune system, exhibit anti-tumorigenic properties, regulate blood glucose and lipid levels, provide neuroprotection, and exhibit anti-radiation effects [44, 45].

2.8 | Volatile Oils

Volatile oils, commonly referred to as essential oils, are a distinctive class of aromatic, oily liquids found within plants [46]. Typically, volatile oils are sequestered within the plant's epidermis as discrete oil droplets, or they may be associated with resins within the plant's resin ducts. These oils can be extracted through the process of steam distillation, where water vapor facilitates the separation of the oils from the plant material. Examples of such oils include peppermint oil, eucalyptus oil, cinnamon oil, and others. The molecular composition of volatile oils is both intricate and heterogeneous, predominantly consisting of terpenoids, aliphatic compounds, and aromatic compounds. These chemical entities are often linked together through C—C bonds, forming intricate ring structures that contribute to the oils' unique characteristics. The operational attributes of volatile oils are commonly attributed to specific structural elements within their molecular framework, such as the existence of double bonds, the configuration of ring structures, and the nature of functional groups. The biological effects of volatile oils are manifold, including antibacterial, antiviral, anti-inflammatory, analgesic, antipruritic, sedative, antitussive, and antiasthmatic properties [47, 48]. The precise mechanism of

action for each oil can vary, but often involves interactions with cellular receptors or enzymatic pathways, thereby eliciting the desired therapeutic response.

3 | Polymers

Polymers are complex materials composed of repeating monomer units arranged in a chain-like structure. These molecules exhibit the variability of molecular weights primarily stemming from differences in the number of monomer units present. The molecular structure of polymers is highly variable and customizable, which accounts for the diverse properties exhibited by these materials. Variations in the backbone structure, molecular mass and its distribution, side-chain substituents, and the dispersity of polymer molecules significantly influence the energy band structure, solubility, aggregation, mechanical strength, and other material properties [49]. Moreover, the design and manipulation of the morphology and structure of polymer molecules are crucial strategies for modifying their properties. Polymers are widely utilized due to their versatility, safety, and wide range of choices, making them the preferred choice to conjugate with active ingredients from TCM.

Polymers are primarily divided into two broad types according to their origin: natural polymers and synthetic polymers as shown in Figure 3. Natural polymers, like chitosan, gelatin, sodium alginate (SA), and starch, have been extensively explored for encapsulating and delivering active ingredients and other bioactive molecules. Their biocompatibility, controlled enzymatic degradation, specific interactions with biomolecules, and ease of modification make them highly suitable for applications in TCM. Synthetic polymers, on the other hand, are typically produced through chemical synthesis methods, which allows for greater design flexibility, reproducibility, and versatility. These polymers have been integral to the advancement of TCM, widely employed in loading small molecules of TCM, which offer tailored solutions for targeted and efficient pharmacological actions [50]. The following research exemplifies the extensive utilization and varied applications of polymers in TCM and pharmaceutical science, underscoring their ability to boost the efficacy and safety of TCM through sophisticated integration strategies.

3.1 | Natural Polymers

3.1.1 | Chitosan (CS)

CS is primarily extracted from the shells of crustaceans like shrimp and crabs. It is a derivative of chitin, the second most abundant polysaccharide in nature, obtained through the deacetylation process that entails the elimination of acetyl groups from chitin molecules [51, 52]. The deacetylation process yields the molecular structure of CS, which consists of repeating units of D-glucosamine and N-acetyl-D-glucosamine linked by β-1,4-glycosidic bonds [53, 54]. CS exhibits outstanding biocompatibility, biodegradability, non-toxicity, and

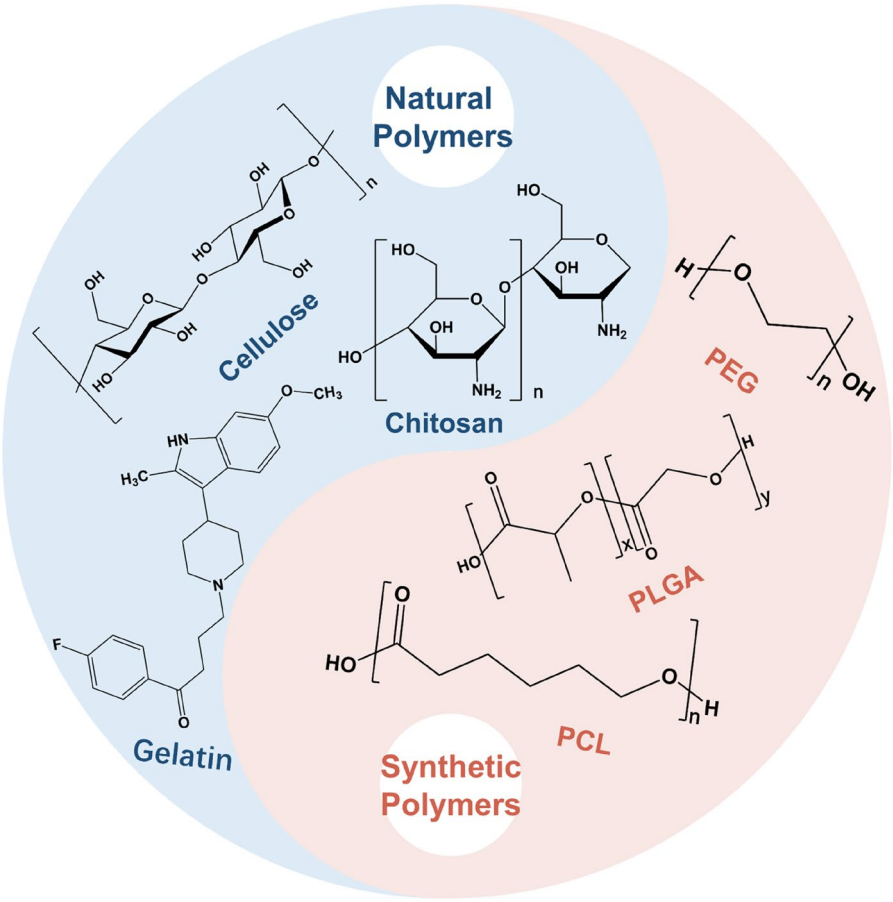

FIGURE 3 | Two broad types of polymers, including natural polymers and synthetic polymers.

positively charged, which allows it to interact effectively with negatively charged components in TCM. This interaction enhances the stability of the active ingredients, preventing their rapid degradation within the body. Additionally, the ability to control the cross-linking degree of CS enables the sustained release of effective ingredients, thereby prolonging the therapeutic effect and reducing the frequency of dosing [55]. In the domain of drug delivery systems, CS has been transformed into various formats, including NPs, microspheres, and hydrogels, suitable for applications in tablets, films, external powders, and other dosage forms [56–60]. For instance, Zhao and colleagues have synthesized hydrogels based on carboxymethyl CS and dialdehyde dextran grafted natural borneol, utilizing Schiff base cross-linking for their antibacterial properties [61]. Similarly, Wang et al. have developed a CS/silk fibroin sponge scaffold loaded with natural carbonized rhubarb, aimed at promoting diabetic wound healing [62]. Additionally, Chen et al. have fabricated a novel nanoaggregate for breast cancer therapy, employing oleanolic quaternary ammonium driven by electrostatic interactions, which was subsequently introduced into heparin and coated with CS for strong anti-leakage characteristics [63].

3.1.2 | Gelatin

Gelatin, a versatile protein, is predominantly derived from collagen, a structural protein discovered in the connective tissues of animals. Collagen is a fundamental component of animal skins and bones, providing strength and flexibility to tissues [64]. The production of gelatin involves chemical treatments like enzymatic and acid hydrolysis, which break down collagen into its constituent amino acids. The molecular structure of gelatin is characterized by its amino acid compositions linked by β-1,4-glycosidic bonds [65]. This unique structure endows gelatin with a scope of physical and chemical properties, including surface activity, film-forming capabilities, adjustable porous structure, and a reversible denaturation process that occurs in both gel and sol states, which make gelatin a valuable commercial protein in biomedical applications. Specifically, gelatin is employed in various capacities, such as an adhesive, capsule material, and carrier in oral formulations [66]. Furthermore, its use extends to suppositories, where its physical properties allow for effective combination with active ingredients. In the realm of tissue engineering and wound healing, researchers have utilized gelatin's biocompatibility and structural integrity to prepare polycaprolactone (PCL)/gelatin electrospun fibers [67]. Besides, Wu et al. have developed a PCL/gelatin nanofiber membrane loaded with cryptotanshinone and salidroside, which jointly promotes vascularization and osteogenesis [68]. Additionally, gelatin has been employed as the adhesive substrate in polymer swelling needles, which are used to deliver matrine for the treatment of eczema, significantly alleviating symptoms [69].

3.1.3 | Cellulose

Cellulose, a fundamental component of plant cell walls, is prevalent in various natural resources such as wood, cotton, corn, and wheat. It is composed of glucose units linked together by β-1,4-glycosidic bonds [70, 71]. The molecular structure of cellulose is characterized by its long chains of glucose units, which are interconnected by hydrogen bonds, forming microfibrils. These microfibrils further assemble into cellulose crystals, characterized by their high crystallinity, making cellulose inherently insoluble in water but can be enhanced through chemical modification. Through chemical or physical modification of natural cellulose, a variety of cellulose derivatives with specific properties can be obtained, which expands the potential applications of cellulose as a candidate in the active ingredients from TCM. The innovation in this field lies in the modification of nanocellulose structure and the integration of various materials to create targeted, gastric retention, lipophilic, controlled, or sustained polymer systems [72–74]. Cellulose filter paper, for instance, is a popular choice for the immobilization of enzymes like α-glucosidase and can be utilized in the screening of inhibitors from TCM [75, 76]. Xing et al. have demonstrated the use of cellulose nanocrystals and polydopamine to coat dendritic mesoporous organosilica NPs, thereby developing biocompatible and pH-responsive nanocarriers for the effective delivery of PTX [77]. Moreover, cellulose nanocrystals have been employed as nanocarriers to simultaneously load curcumin and folic acid, enhancing the therapeutic efficacy and selectivity of these compounds [78].

3.1.4 | Silk Fibroin (SF)

SF, a component of silk, is produced by silkworm pupae in their silk glands. Its molecular structure is primarily composed of amino acids linked by β-1,4-glycosidic bonds, with glycine and alanine being the predominant amino acids [79]. SF is renowned for its excellent mechanical strength and toughness, along with its ease of purification, modification, and functionalization. It also possesses a highly porous structure, which facilitates the loading and controlled release of active ingredients. SF-based NPs, hydrogels, microspheres, and fiber membranes have been developed as versatile platforms loading active molecules, including drug monomers, proteins, peptides, and nucleic acid drugs [80–82]. They work effectively to enhance the encapsulation rates, reduce degradation, control drug release, and minimize adverse reactions. Specifically, Zhang et al. have designed a sealant agent based on the combination of silk protein and Rehmanniae Radix Preparata to accelerate skin repair [83]. Besides, a supramolecular hydrogel antibacterial dressing has been proposed, in which puerarin is interconnected with a secondary macromolecular SF nanofibrillar network for the treatment of infected wounds [84]. Moreover, Wang's group has introduced a novel hierarchical drug delivery system for osteoarthritis therapy, featuring a micrometer-scale outer layer of spheres composed of regenerated SF with a connected porous structure [85].

3.1.5 | Other Natural Polymers

Beyond the previously mentioned polymers, numerous other natural ones have also been utilized in pharmaceutical applications. Collagen, a polymer derived from animal connective tissues like skin, bones, and muscles, is highly valued for its exceptional biocompatibility and low immunogenicity. Collagen's

molecular structure is composed of long chains of amino acids connected by peptide bonds, and it contains amino acids linked by α-1,3-glycosidic bonds. Researchers have explored collagen's potential in various applications, such as Wang and colleagues' fabrication of a collagen film containing resveratrol and celastrol (Cela) to research the growth of human periodontal ligament fibroblasts and the differentiation of bone marrow macrophages into osteoclasts [86]. Tang et al. have synthesized an epoxidized *Bletilla striata* polysaccharide that crosslinks with collagen to create a novel hemostatic sponge [87]. SA, a biocompatible polyelectrolyte with high charge density, can form a polymer network through calcium ion cross-linking. SA is utilized as a matrix for preparing solid dispersions containing Tanshinone IIA (TA) to enhance its dissolution rate, in vivo bioavailability, and pharmacological activity [88]. Li et al. have combined SA with hyaluronic acid (HA) to construct a composite hydrogel scaffold that incorporates extracellular vesicles and Icariin, aiming to promote cartilage regeneration [89]. Starch, primarily derived from the seeds, roots, stems, and other plant parts such as wheat, corn, and potatoes, is composed of glucose units linked by α-1,4-glycosidic bonds. It is extensively used in the pharmaceutical industry for the controlled release of active ingredients. Luan et al. have devised a natural microneedles drug delivery system using gelatinized starch and two Chinese herbal ingredients, *aloe vera* and berberine, for wound repair [90]. Additionally, porous starch has been employed as a solid carrier material to solidify liquid volatile oils through physical adsorption [91].

3.2 | Synthetic Polymers

3.2.1 | Polyethylene Glycol (PEG)

PEG constitutes a polymer made up of numerous ethylene glycol units linked through ether bonds. This repetitive ether bond structure confers PEG with exceptional water solubility and non-toxic properties. In the biomedical sector, PEG has emerged as a gold standard and is frequently utilized in conjunction with other substances, such as polymers like PCL, polylactic-co-glycolic acid (PLGA), and artificial biomembrane liposomes [92]. Particularly noteworthy is the role of the PEG shell in protecting particles from aggregation, immune recognition, and phagocytosis, thereby extending their circulation time within the body. The integration of PEG with the active ingredients from TCM is a prevalent strategy to enhance delivery efficacy and in vivo pharmacokinetics. In detail, Jiang et al. have developed a pH-responsive nano platform comprising mesoporous silica NPs loaded with Arsenic trioxide. They achieved pH-triggered release and regulated CD 8^+ T cells and T_{reg} cells in the tumor microenvironment by grafting PEG onto the NPs [93]. Hao et al. have designed reactive oxygen species (ROS)-responsive micelles to deliver resveratrol for treating liver fibrosis. These micelles were prepared using a ROS-responsive amphiphilic block copolymer as the core and a PEG shell modified with a peptide insertion [94]. Similarly, Hu and colleagues have utilized PEG to modify magnetic graphene oxide, thereby enhancing its stability in physiological solutions. This modification led to the creation of a high-performance cell membrane biomimetic graphene nano decoy that improved the screening efficiency of active components from TCM [17].

3.2.2 | PLGA

PLGA is a biocompatible copolymer synthesized through the polymerization of lactic acid (LA) and glycolic acid (GA) monomers. Its molecular structure is characterized by the presence of alternating LA and GA units, which are joined by ester bonds. PLGA exhibits several desirable properties, including excellent biocompatibility, biodegradability, low immunogenicity, low toxicity, and good mechanical strength. These attributes have led to its approval by the U.S. Food and Drug Administration (FDA) for use as a controlled-release drug carrier. PLGA has been effectively utilized in the formulation of various dosage forms to load both fat-soluble and water-soluble active ingredients from TCM. These dosage forms encompass micelles, NPs, microspheres, gels, and more, effectively addressing the inherent limitations of active ingredients [95–98]. An illustrative example is the use of PLGA as an NP carrier, integrated with cationic lipid, to encapsulate magnolol. This approach resulted in a significant anti-ulcerative colitis effect following oral administration [99]. In the field of bone regeneration, PLGA-based porous composites were synthesized by leveraging the osteogenic ability of bioactive glass particles and the osteogenic and osteoclastic properties of neferine [100]. Additionally, Gu et al. fabricated PLGA/β-TCP scaffolds modified with $Ti_3C_2T_x$@PLGA/Icaritin microspheres, which demonstrate near-infrared response and enhance bone regeneration [101].

3.2.3 | PCL

PCL is a polymer synthesized from caprolactone monomers through a polymerization process. Its molecular structure is composed of repeating caprolactone units, which are derived from petrochemical raw materials and are connected by ester bonds. PCL possesses a prolonged degradation cycle, which allows it to form more stable microspheres and NPs. The copolymerization of PCL with other polymers such as poly(l-lactide) (PLA) and PLGA can influence its physicochemical properties, thereby enhancing its performance across a broad spectrum of applications. Several PCL-based products have been approved by the U.S. FDA and are clinically applicable. In the domain of TCM delivery, numerous PCL-based systems have been developed, including hydrogels, micelles, and microspheres [102–104]. Feng and colleagues, for example, have fabricated SF/PCL fibrous membranes loaded with *Psoralea corylifolia* formula for the treatment of colorectal cancer. They utilized coaxial electrospinning to create core-shell dual drug-loaded fibers, encapsulating Ganoderma lucidum triterpenoids within them to address cervical cancer [105]. Tang et al. have designed a 3D-printed PCL stent loaded with Panax notoginseng saponin, which exhibits the ability to promote re-endothelialization and reduce local inflammation in the carotid artery of rabbits [106].

3.2.4 | Other Synthetic Polymers

The utilization of synthetic polymer-based systems often involves the integration of multiple materials to achieve functional diversity and enhancement. These composite systems are designed to compensate for the limitations of individual

substances while potentially introducing new beneficial properties.

In this regard, Wang et al. have examined the impact of periostracum cicadae extract and N-acetyl dopamine compounds on improving sleep disturbances. Their research demonstrated that both substances effectively improved the hypothalamic pathology associated with insomnia in rats, thereby enhancing sleep quality in these animals [107]. In addition, Chen's team has crafted dual pH- and reduction-sensitive crosslinked polymeric micelles intended for the delivery of paclitaxel. The micelles are constructed from a polymer network composed of three segments: polyethylene glycol methyl ether methacrylate, disulfide, and poly(ε-caprolactone-co-γ-amine-ε-caprolactone) connected by disulfide bonds [108]. Based on L-methionine poly (ester amide), a novel ROS-responsive system was developed, which self-assembles into nano-micellar-type NPs, offering potential as a carrier for anticancer drug delivery [109]. FA-modified Cela NPs were encapsulated within a PVP-co-2-dimethylaminoethyl methacrylate polymer to enhance their anticancer activity [110]. Based on poloxamer, Jing and colleagues have created a Fructus Xanthii and Magnolia liliiflora volatile oils liposomes-loaded thermosensitive in situ gel. This system effectively manages allergic rhinitis [111].

The examples mentioned above illustrate the extensive use and diverse applications of both natural and synthetic polymers in the field of TCM and pharmaceutical science, underscoring their potential to enhance the efficacy and safety of TCM through advanced polymer-based systems.

Overall, the utilization of both natural and synthetic polymers in the active ingredients from TCM is gaining growing acknowledgment. Table 1 provides a synopsis of instances highlighting their specific applications. In contrast, significant distinctions exist between natural and synthetic polymers concerning their origins, synthesis techniques, application scenarios, and attributes. Natural polymers, typically sourced from natural origins, exhibit favorable biocompatibility, reduced toxicity, and environmental friendliness. Consequently, they are deemed relatively safe for application in TCM. Nonetheless, natural polymers may perform poorly in terms of mechanical robustness and stability, and the variability of qualities of naturally derived materials can impact the combination efficacy with active ingredients from TCM. Synthetic polymers, on the other hand, offer the advantage of customizable molecular structures and properties to meet specific requirements, generally possessing superior mechanical properties and stability. The precise control over molecular weight and structure in synthetic polymers makes them ideal for the controlled release of active ingredients. However, some synthetic polymers may raise concerns regarding biocompatibility, non-biodegradability, and environmental hazards. Hence, the challenge lies in harnessing their strengths while mitigating the limitations, a consideration that must be addressed in future research endeavors.

4 | Design Strategies and Applications of Polymers

Given the challenges associated with the active ingredients from TCM, the application of polymers has emerged as an encouraging strategy for loading, modifying, detecting, or conjugating these substances, capitalizing on the diversity of polymer molecular types, structures, and the adjustability of their physical and chemical properties. This versatility allows polymers to interact with active ingredients in various ways, including physical adsorption, chemical bonding, encapsulation, covalent bonding, electrostatic interactions, and water transport mechanisms. Through these mechanisms, polymers effectively load active ingredients, thereby enhancing stability, safety, bioavailability, therapeutic effects, and prolonging efficacy. Additionally, polymers can be carefully selected and designed based on the properties of the drug, treatment requirements, and administration routes. This can involve the use of MIPs, polymer NPs, polymer micelles, polymer hydrogels, polymer conjugates, and so on, all aimed at breaking through the bottleneck of TCM via effectively detecting and extracting active ingredients, controlling drug release, improving bioavailability, and prolonging drug efficacy. As research in this field continues to advance, the understanding of how polymers interact with active ingredients from TCM will further evolve, offering new possibilities for the modernization and precision treatment of TCM. This development is pivotal in harnessing the full potential of TCM in contemporary medical applications.

4.1 | MIPs

MIPs are artificially engineered receptors that are tailored to specifically recognize and bind to a particular target molecule using molecular imprinting technology. These polymers exhibit a remarkable ability to selectively identify and interact with their target molecules, even amidst complex mixtures and in the presence of various interfering substances [12]. The key to selective recognition by MIPs lies in the precise design of their imprinted cavities, which are meticulously crafted to match the molecular size, chemical properties, and spatial structure of the template molecule. This molecular mimicry creates a beneficial molecular memory effect, enabling MIPs to selectively bind to and recognize the target molecules, much like antibodies in biological systems. This selective recognition property of MIPs renders them highly advantageous in the identification and combination of active ingredients from TCM [112]. They serve as “artificial antibodies” in this context, offering a powerful tool for the identification, extraction, and separation of active ingredients. This section will delve into the applications of MIP technology in these aspects.

MIPs can indeed serve as an effective standalone strategy due to their high sensitivity to specific components in TCM. In this regard, Fu et al. have designed a bioenzyme-induced MIP system, optimized theoretically, to serve as an electrochemical sensor dedicated to the precise quantification of protocatechic acid (PA) (as shown in Figure 4a). Employing $LaFeO_3$ nanospheres as substrates and bovine hemoglobin anchored on the surface, they initiated the polymerization to get MIPs. Methacrylic acid (MAA) with methyl ester group was identified as the optimal functional monomer through computational screening, capable of complexing with PA via a robust single hydrogen bond interaction. This interaction mechanism enables the sensor to respond more swiftly and precisely to free PA, which is selectively captured by hydrogen bonds within the MIPs' recognition cavity, unaffected

TABLE 1 | Specific application instances of natural and synthetic polymers in TCM.

Type	Main body	Form	Properties/functions	Application	References
Natural polymers	Carboxymethyl CS	Hydrogel	Injectability and antibacterial ability	Treating topical wound infections.	[61]
	PCL/gelatin	Nanofiber membrane	Long-term and spatially targeted drug release	Promoting angiogenesis and bone repair	[67]
	Cellulose	Nanocarriers	pH-sensitive, controllable drug release, and efficient ROS generation	Enhancing chemodynamic cancer therapy	[77]
	SF	Nanofibrillar hydrogel	Antioxidation, antibacterial activity, and hemostasis	Treating infected wound	[84]
	Collagen	Sponge	Excellent hemostatic performance	Hemostatic care and wound healing	[87]
	SA	Solid dispersion	Anti-inflammation	Improving the pharmacological activity of TA	[88]
	Gelatinized starch	Hydrogel microneedle patches	Antibacterial activity, anti-inflammation; fibroblast-growth promotion and adjustable mechanical properties	Wound healing	[90]
Synthetic polymers	A PEG shell and a block copolymer	Micelles	Alleviating inflammatory infiltration, preventing fibrosis, and protecting hepatocytes	Ameliorate liver fibrosis	[94]
	PLGA/icaritin	Microspheres-modified scaffolds	Photothermal ability and osteogenic capacity	Enhancing bone regeneration	[101]
	SF/PCL	Fibrous membrane	Degradability, sustained drug release, and anti-tumor properties.	Treating colorectal cancer	[105]
	N-Acetyl dopamine	Polymeric compounds	Affecting expression of neurotransmitter and protein	Improving PCPA-induced insomnia	[107]
	Polyethylene glycol methyl ether methacrylate-disulfide-poly(ε-caprolactone) -co-γ-amine−ε-caprolactone polymers	Micelles	Inhibitory effect on HepG2 cells and dual pH/reduction-response	Promoting PTX delivery	[108]
	Poly(ester amide)	Polymeric nanoparticles	Oxidation response, biodegradability, and biological activity	Enhancing anticancer drug delivery	[109]
	PVP-co-2-dimethylaminoethyl methacrylate	Nanoparticles	Low colony-forming assay unit, killing activity, and apoptosis-inducing ability	Treating breast cancer	[110]
	Poloxamer	In situ gel	Good water solubility, low toxicity and irritation, inflammatory control ability, and suitable gel effect	Allergic rhinitis management	[111]

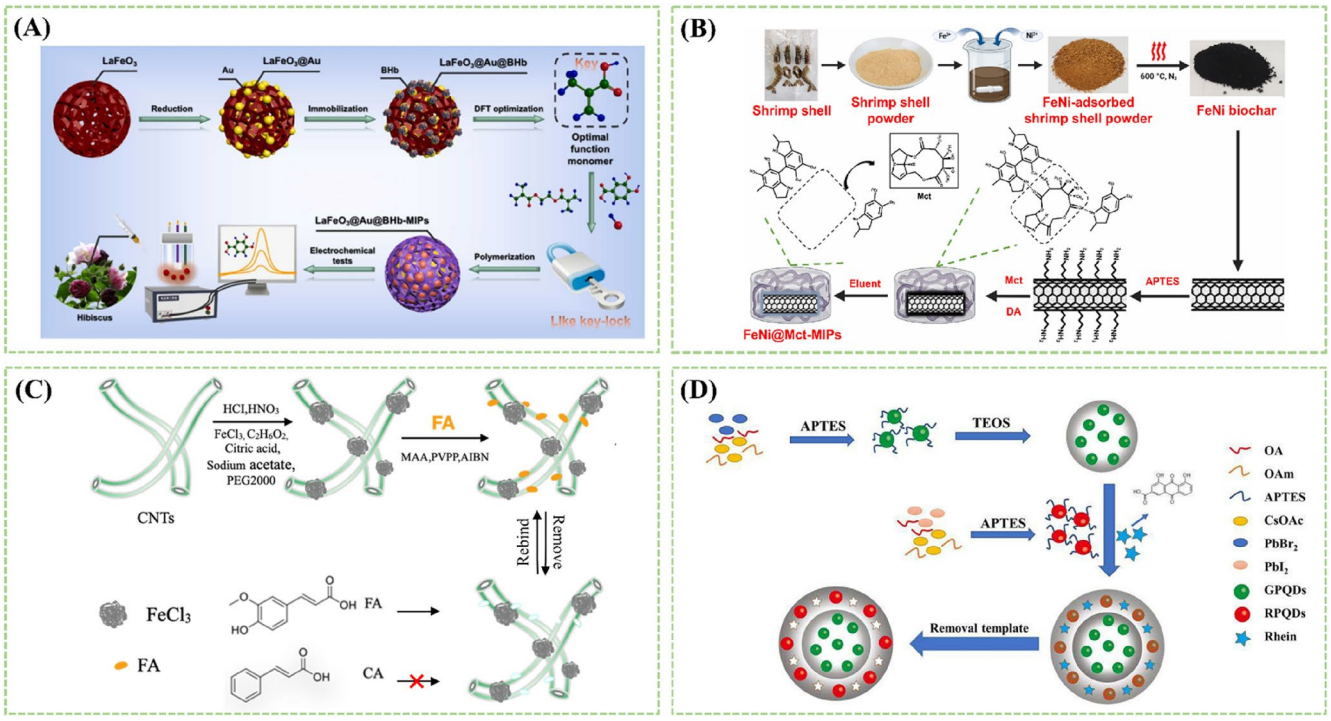

FIGURE 4 | Molecularly imprinted polymers (MIPs). (A) A bioenzyme-induced MIP system as an electrochemical sensor to quantify the PA. Reproduced with permission [11]. Copyright 2023, published by Elsevier. (B) A metal coordination-synergistic imprinted polymer to identify and separate monocrotaline. Reproduced with permission [113]. Copyright 2023, published by Elsevier. (C) A MIP with MCNTs carrier for the enrichment and determination of FA along with HPLC technology. Reproduced with permission [116]. Copyright 2021, published by Elsevier. (D) A fluorescent probe consisting of red and green perovskite QDs to visibly and fluorescently detect Rhein. Reproduced with permission [119]. Copyright 2023, published by Elsevier.

by other contaminants. Consequently, the sensor exhibits an expansive linear response range from 0.2 to 1000 μM and an impressive low limit of detection (LOD) at 55 nM [11]. Ge et al. have synthesized a metal coordination-synergistic imprinted polymer (FeNi@Mct-MIPs) that is anchored onto FeNi biochar, facilitating the identification and separation of the poisonous compound monocrotaline from herbal medicines (see Figure 4b). The FeNi biochar, serving as a magnetic scaffold under an external magnetic field, was overlaid with a molecularly imprinted layer through the self-polymerization of dopamine to function as a solid-phase extraction adsorbent. Owing to the moderate alkalinity, the conjugation formed with the detection system, and the appropriate molecular size of Mct, FeNi@Mct-MIPs demonstrated unparalleled selectivity and the highest adsorption capacity for Mct among various alkaloids, reaching an adsorption capacity of 64.59 mg g^{-1} [113]. Besides, Chen and partners have developed a novel magnetic-MIP (MMIP) with the specific ability to recognize tripterine. This MMIP is composed of a magnetic component derived from graphene oxide and Fe_3O_4 NPs anchored on a silica shell, which allows for quick and selective adsorption of tripterine. The MMIP exhibits a significantly higher maximum adsorption amount (30.65 mg g^{-1}) compared to non-imprinted polymers (13.47 mg g^{-1}). Additionally, the MMIP demonstrates a superior binding behavior with tripterine compared to several other active constituents, showcasing its exceptional recognition and selection properties for tripterine [114].

Moreover, MIPs can be effectively integrated with other technologies to enhance their functionality and application scope. For instance, Guo et al. have developed a thermosensitive MIP that is combined with high-performance liquid chromatography (HPLC) to quantify quinolizidine alkaloids in the extracts of *Sophora flavescens*. This system harnesses the critical phase transition properties of the polymers, in conjunction with the robust ionic and hydrogen bonding forces between the bifunctional monomers to achieve temperature-sensitive and selective adsorption/release properties. The temperature-induced dissociation between monomers at elevated temperatures allows the polymers to exhibit enhanced adsorption capacity. By employing temperature and solvent variations in the solid-phase extraction process, the concentration of quinolizidine alkaloids can be substantially enhanced up to 5.2 times the origin [115]. Fu et al. have synthesized an MIP utilizing magnetic carbon nanotubes (MCNTs) as the supporting matrix for the enrichment and determination of FA along with HPLC technology (see Figure 4c). The MCNTs@FA-MIPs are synthesized via a non-covalent interaction approach, with FA serving as the template, which yields a substantial adsorption capability (50 mg g^{-1}), swift separation kinetics, and superior selectivity toward FA. In contrast to MCNTs@NIPs, MCNTs@FA-MIPs exhibit a markedly enhanced adsorption capacity, possibly due to the presence of multiple specific adsorption sites on their surface. Additionally, MCNTs@FA-MIPs achieve adsorption equilibrium more rapidly. This exceptional uptake response can be ascribed to the continuous occupation of the finite recognition sites by FA molecules, facilitating a swift and precise quantification of FA [116]. The combination of MIT with quantum dots (QDs) leverages the

superior specificity of MIPs alongside the outstanding optical and electrochemical attributes of QDs [117, 118]. For instance, Zhu et al. have synthesized a fluorescent probe capable of visibly and fluorescently detecting Rhein (see Figure 4d). This composite consists of red and green perovskite QDs, with Rhein serving as the templating molecule and SiO_2 as the encapsulating layer. The MIPs@RPQDs/GPQDs@SiO_2 surface is rich in imprinted cavities that selectively recognize rhein, effectively quenching the fluorescence of RPQDs via interactions between rhein and the composite material. This interaction induces a fluorescence color shift from red to blue-green. Furthermore, UV absorption spectra reveal the formation of a new complex resulting from the rhein-system interaction, corroborating the static quenching mechanism. This assay exhibits a robust linear correlation with rhein concentration and achieves a LOD of 1.90 nM [119]. Moreover, Ye et al. have crafted a molecularly imprinted ratiometric fluorescent sensor aimed at quantifying aristolochic acid I (AAI), which is founded on the Schiff base fluorescent material N, N′-bis(o-carboxybenzylidene)-p-4,4′-diaminobiphenyl (BDDB). BDDB is encapsulated within silica NPs (BDDB@SiO_2) functioning as a blue-fluorescent reference standard, whereas yellow-emitting cadmium sulfide QDs act as the responsive fluorescent material. The MIP encapsulation of these materials results in a probe that undergoes a fluorescent color shift from yellow to green and finally to blue upon exposure to AAI [120]. Additionally, Zhang's group has encapsulated carbon nanodots into MIPs to form a ratiometric fluorescence probe. This probe utilizes the mechanisms of static quenching and the inner filter effect to detect furazolidone selectively across a concentration span of 5–400 mg L^{-1}, achieving an LOD of 1.98 mg L^{-1} [121].

4.2 | Polymer NPs

The emergence and advancement of nanotechnology have significantly broadened the research landscape within the realm of nanomedicine, particularly within the sphere of TCM. NPs, due to their unique scale structure, have demonstrated exceptional application potential in TCM. These particles are typically categorized into several types, including polymer NPs, metal NPs (such as gold and silver NPs), liposome NPs, and inorganic NPs. Polymer NPs, in particular, possess suitable structures and particle sizes that allow for precise control of drug loading and release. Additionally, they feature convenient availability, outstanding biocompatibility, and minimal toxicity, rendering them highly appropriate for combining with active ingredients from TCM. These characteristics are crucial for the development of effective and safe TCM formulations, especially when aiming to enhance their therapeutic efficacy and bioavailability.

Particularly, some of these polymer NPs, such as PLGA and PEG, have already gained approval from the U.S. FDA and are entering clinical applications. To enhance the therapeutic efficacy of isoliensinine, Yao et al. proposed its encapsulation within PEG-PLGA polymer NPs (as shown in Figure 5a). The PEG-PLGA@Isoliensinine formulation was prepared using the nano-precipitation method, and its superiority over free isoliensinine in treating hypertension was confirmed through comprehensive assessments. The findings indicate that PEG-PLGA@Isoliensinine shows a superior cellular uptake rate compared to free Isoliensinine. Additionally, it potentiates the antihypertensive and antiproliferative effects on vascular smooth muscle cells via the PI3K/AKT signaling pathway. Besides, the advantages of PEG-PLGA NPs include increased solubility of lipophilic drugs, enhanced drug stability, and prolonged retention time in the gastrointestinal tract. Moreover, the encapsulation within the NPs effectively reduced the release rate of isoliensinine, thereby enhancing drug release control and improving therapeutic outcomes [14]. Furthermore, a novel pH-sensitive, targeted drug delivery system has been developed, employing NPs encapsulating astragalus polysaccharides (APS) (see Figure 5b). The ovalbumin-loaded, pH-sensitive APS-coated PLGA NPs were fabricated through the multiple emulsion solvent evaporation technique. This pH-responsive property makes the system exert effects much more quickly than normal drug formulations and shows stronger intracellular targeting during the early stages of immunization. Moreover, these PLGA NPs demonstrated superior capabilities in ovalbumin release across varying pH conditions and effectively enhanced both cellular and humoral immune responses during the initial stages of immunization [122]. Wang et al. have engineered biodegradable PEG-block-poly(trimethylene carbonate) (PEG-PTMC) NPs (PPNPs) as a delivery vehicle for Ginkgolide B (GB), a powerful therapeutic for Parkinson's disease (PD). GB was incorporated into PEG-PTMC via an antisolvent precipitation technique, yielding GB-loaded PPNPs. These NPs possess a negative surface charge, maintain a highly stable structure, and demonstrate biocompatibility. In comparison to free GB, GB-PPNPs show elevated levels of GB in both plasma and brain tissue, attributed to improved uptake efficiency. This development provides an oral delivery mode for PD treatment [123]. Besides, Ren et al. have proposed a gene therapy strategy for cancer treatment using lysenin. The NP formulation they developed comprises self-assembled biodegradable polymers, mPEG-PDLLA and N-[1-(2,3-dioleoyloxy)propyl]-N, N, N-trimethylammonium chloride, which encapsulate a plasmid vector encoding the therapeutic gene. Lysenin gene therapy induces necrosis and autophagy in tumor cells, directly killing them, and also stimulates antitumor immunity. This formulation effectively inhibits tumors without causing obvious adverse effects and demonstrates potential for clinical application in cancer therapy [124].

The development of various types of polymers for the preparation of NPs has significantly expanded the range of options available for active ingredient delivery and formulation. Feng et al. have constructed sulfasalazine (SK)-loaded ES100/HA/CS NPs (SK@SAC) to serve as an oral drug delivery platform for treating inflammatory bowel diseases (IBD) (Figure 5c). This system entails the surface modification of CS NPs using HA and incorporating a targeting agent, CD44, which binds to the CD44 receptor on cells. The SK@SAC system markedly diminished accumulation in the spleen and kidneys, indicating effective prevention of systemic biodistribution and potential toxicity. Besides, the internalization of the NPs by macrophages and colon epithelial cells was augmented because of the targeting effect of HA on CD44 receptors. The antioxidant efficacy of SK@SAC is likely attributed to the enhanced metabolism of lipid peroxidation, and this targeted delivery decreases the influx of immune cells into the inflamed region, thereby potentially enhancing the integrity of the intestinal barrier via oral administration [125]. As shown

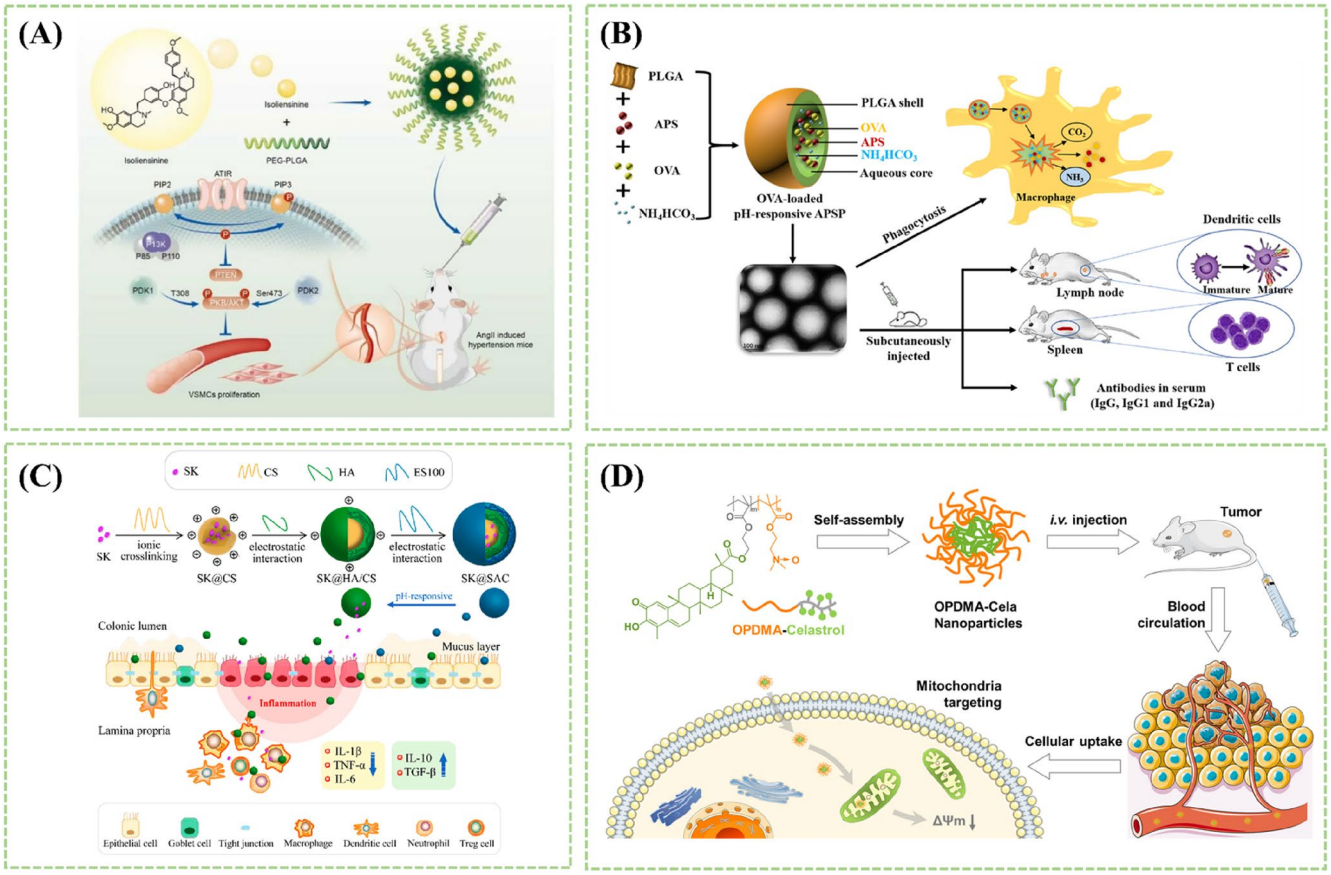

FIGURE 5 | Polymer NPs. (A) The PEG-PLGA@Isoliensinine NPs prepared by nano-precipitation for the treatment of hypertension. Reproduced under terms of the CC-BY license [14]. Copyright 2024, published by Elsevier. (B) A novel pH-responsive targeting drug delivery carriers using PLGA with APS encapsulated inside to enhance immune responses. Reproduced with permission [122]. Copyright 2022, published by Elsevier. (C) The SK@SAC NPs as an oral delivery system to treat colitis mice. Reproduced under terms of the CC-BY license [125]. Copyright 2022, published by Royal Society of Chemistry. (D) A block copolymer carrier for Cela delivery. Reproduced with permission [126]. Copyright 2022, published by Elsevier.

in Figure 5d, Geng and colleagues employed a block copolymer consisting of poly(2-(N-oxide-N, N-dimethylamino)ethyl methacrylate)-block-poly(2-hydroxyethyl methacrylate) to produce a conjugate through the process of reversible addition-fragmentation chain transfer polymerization. By incorporating Cela into this polymer, a polymer-Cela conjugate was synthesized capable of self-assembling into NPs when introduced to aqueous media. This self-assembly is facilitated by hydrophobic interactions and π-π stacking, a consequence of the conjugate's amphiphilic character and the rich array of aromatic rings in the core. The pH-sensitive release of Cela is achieved via acid/base-catalyzed hydrolysis of the ester bonds. This conjugate nanoparticle significantly improves the water solubility of Cela, ensures rapid blood clearance, and enhances tumor-targeting efficacy, all while maintaining minimal toxicity. Consequently, the conjugate NP exhibits a more potent anticancer efficacy compared to free Cela [126]. A novel biopolymer-based NP system was designed taking casein as the carrier and modifying it with menthol to serve as a brain-targeting ligand. This conjugate was formed based on the amphiphilic structure of casein, which facilitated drug-induced self-assembly for the preparation of casein NPs. Subsequently, the anti-cancer drug 10-hydroxycamptothecin (HCPT) was loaded into these NPs. The findings of this research demonstrated that the biopolymer-derived NP substantially increased the concentration of the drug in the tumor area. This targeted delivery led to a prolonged median survival duration for mice with intracranial gliomas [127].

4.3 | Polymer Micelles

Polymer micelles constitute stable colloidal systems that arise from the spontaneous assembly of synthetic amphiphilic block copolymers within aqueous environments. Over the past few years, they have emerged as a promising drug delivery platform for therapeutic compounds, particularly for those that are insoluble, have high potency, and significant toxicity. The encapsulation of such compounds within polymer micelles has demonstrated improved pharmacokinetic profiles and enhanced efficacy in preclinical animal models, with superior safety profiles compared to traditional formulations. This section primarily delves into the synthesis and design of block copolymers for creating polymer micelles, the comprehensive examination of experimental and theoretical active ingredients encapsulation within these micellar structures, as well as discusses additional pertinent considerations.

Polymer micelles are primarily composed of amphiphilic block copolymers or base materials combined with modifiers. This composition allows for the precise design of the micelles'

hydrophilicity, biocompatibility, and drug-loading capabilities. In this regard, Sun et al. designed an injectable polymeric micelle formulation for the therapeutic administration of Icariside II (ICA II) in cancer chemotherapy treatments. They employed amphiphilic block copolymers synthesized from mPEG-PCL-Phe(Boc), which demonstrated the maximum entrapment efficiency for ICA II. This high efficiency was linked to the interaction occurring between ICA II and the terminal segment of the block copolymer, consisting of L-Phenylalanine (L-Phe). The aromatic rings in L-Phe facilitated intermolecular π-π stacking and hydrogen bonding with ICA II, leading to the formation of a tighter micelle core. The encapsulation of ICA II within these micelles augmented its bioavailability and potentiated its antineoplastic activity, as evidenced by both in vitro and in vivo studies. These studies revealed a marked enhancement in antitumor activity in comparison to the free form of ICA II [128]. Miao et al. fabricated a mannose-functionalized, colon-specific micelle drug delivery system that incorporated QDs and EMO (a therapeutic agent) to create Eu-CS-Man-Ps-P/EMO-QDs. The system utilized Eudragit S100 for pH sensitivity to target the colon, while CS played a role in mucosal adhesion. This micelle could enhance the retention and controlled release of EMO in colonic ulcers by employing a multi-stage targeting strategy, improving oral bioavailability, regulating the expression of inflammatory factors, and repairing damaged tissues, thus achieving the design goal of integrating ulcerative colitis diagnosis and treatment [129]. Besides, Long et al. reported on a redox-sensitive polymeric micelle based on K5 capsular polysaccharide-α-TOS amphiphilic copolymers (KSST) for lung tumor therapy (see Figure 6a). The amphiphilic copolymers self-assembled and encapsulated artesunate (ART) to form drug-loaded micelles (ART/KSST) in an aqueous solution. ART/KSST micelles enhanced the permeability and retention effect when accumulating at the tumor site in the blood circulation. The presence of disulfide bonds in the micelles can be broken by high glutathione concentrations, resulting in fast drug release to effectively kill tumor cells [130]. In addition, Wu et al. designed HCPT polymeric micelles to load Vinegar Radix Bupleuri (VBRB) with enhanced liver-targeting efficiency (see Figure 6b). These polymeric micelles were fabricated by leveraging the solubility variations of HCPT and the CS-based copolymer across diverse pH levels, followed by probe sonication. Hydrophobic interactions and modest ionic forces were the predominant mechanisms driving the enhanced loading and encapsulation

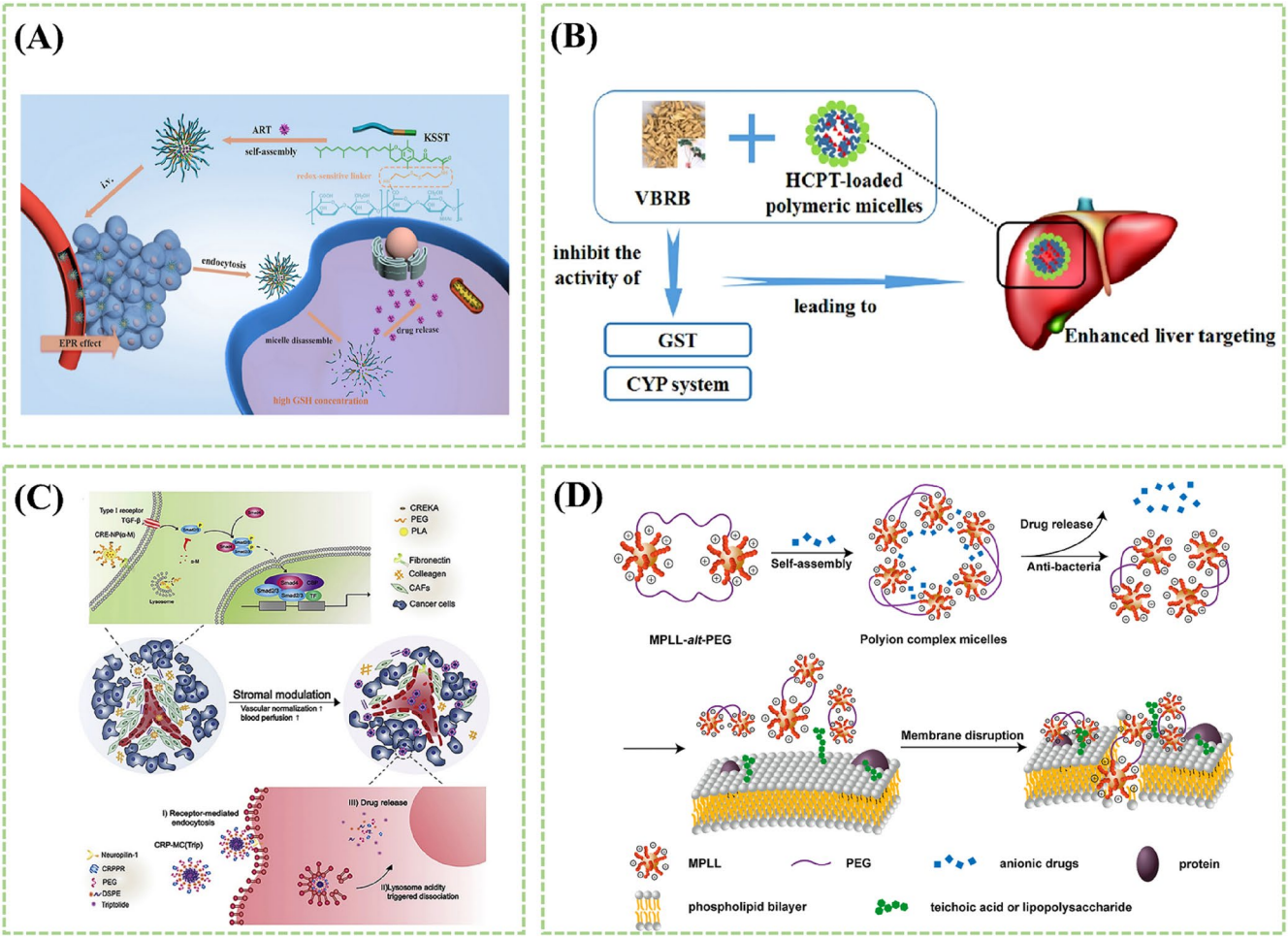

FIGURE 6 | Polymer micelles. (A) A redox-sensitive micelle system encapsulating ART to enhance the therapeutic effect on lung tumors. Reproduced with permission [130]. Copyright 2021, Elsevier. (B) HCPT-loaded polymeric micelles enhancing the liver-targeting efficiency through VBRB after oral coadministration. Reproduced with permission [131]. Copyright 2018, Elsevier. (C) An acidic environment-responsive micelle modified with CRPPR peptide to achieve additional accumulation within the tumor region. Reproduced with permission [132]. Copyright 2020, Elsevier. (D) The copolymers MPLL-alt-PEG as anionic drug delivery vehicles and antimicrobial agents. Reproduced under terms of the CC-BY license [133]. Copyright 2020, published by Multidisciplinary Digital Publishing Institute.

efficiency of HCPT, thereby potentially boosting its oral absorption. The enhanced therapeutic effect can be attributed to the inhibitory action of VBRB on the activity of Glutathione S-transferase (GST), and the suppression of the efflux pump activity of p-glycoprotein, thus overcoming multidrug resistance in tumor cells [131]. Moreover, Feng et al. utilized a PEG–PLA NP matrix to fabricate an acidic environment-responsive micelle, serving as a superior vehicle for triptolide delivery, characterized by reduced toxicity and enhanced therapeutic impact at reduced dosages(see Figure 6c). The micelles were further functionalized with the cell-penetrating CRPPR peptide to augment the targeting of tumor sites. The synthesis protocol involved the ring-opening polymerization of α-amino acid N-carboxyanhydrides, succeeded by an aminolysis reaction. Notably, octadecylamine-p(API-Asp)10 was employed to create acid-sensitive micelles, encapsulating triptolide within their hydrophobic core. This design effectively intensifies the therapeutic efficacy of triptolide while reducing the risk of damage to critical organs [132]. Furthermore, Lu et al. explored the capabilities of PEG crosslinked alternating copolymers multi-branched poly(l-lysine) (MPLL)-alt-PEG as dual-functional entities, serving both as anionic drug delivery vehicles and antimicrobial agents (see Figure 6d). The study showed that the MPLL fragments, possessing a high positive charge density, promoted the electrostatic encapsulation of anionic drug models. This was achieved via the creation of polyion complex micelles featuring an MPLL/drug complex at the core and a crosslinked PEG layer at the periphery, which allowed for pH-dependent drug liberation. The data demonstrate that (MPLL)-alt-PEG is capable of suppressing bacterial growth through a membrane-disruption mechanism, an approach that has garnered extensive recognition as a promising strategy for combating multidrug-resistant bacterial strains [133].

4.4 | Polymer Hydrogels

In recent years, hydrogels have garnered significant attention as carriers for active ingredients from TCM due to their extracellular matrix-like environment, adjustable mechanical properties, and diverse design strategies. The use of hydrogel-coated active ingredients has been shown to enhance their pharmacological activity, and water solubility, and reduce toxicity at lower or equivalent doses compared to the direct application of TCM. Certain molecules derived from TCM can be directly utilized for the synthesis of hydrogels, serving dual roles as carriers and exhibiting pharmacological effects. This section primarily focuses on the conventional polymer-based hydrogel system and active ingredients from the TCM-based hydrogel system.

Typical hydrogels like poly (vinyl alcohol) (PVA), CS, HA, and others, have been extensively and intensively studied. These hydrogels are renowned for their synthesis techniques, unique properties, and diverse applications, particularly in drug delivery systems in TCM. Specifically, Zeng et al. introduced puerarin into CS to create an injectable and self-healing hydrogel (see Figure 7a). The CS@puerarin (C@P) nanofiber hydrogel was fabricated using a one-step grinding technique, resulting in a distinct entangled nanofiber structure and smooth morphology. The nanofibrous architecture of the C@P hydrogel arises from a self-assembly process driven by the interplay of hydrogen bonding and π–π stacking interactions between puerarin and CS solutions, culminating in the emergence of the hydrogel's characteristic porous network.

This hydrogel was found to suppress ectopic miR-29ab1-mediated macrophage activity and regulate inflammation, thereby being beneficial for diabetic wound healing [134]. Besides, Qin et al. encapsulated puerarin into gelatin hydrogel (GelMA) for anti-inflammatory effects and to repair the fascia of the pelvic floor in rabbit models. The Pue@GelMA hydrogel, with its multiple pores micro-structure, promoted cellular adhesion and proliferation. It also exhibited anti-inflammatory effects by reducing the expression of IL-3 and IL-6, suppressing the aggregation of neutrophils and eosinophils, and modulating matrix regeneration/remodeling through the TGF-β/MMPs pathway, thereby preserving a balanced immune milieu [135]. Moreover, Sun et al. developed a hydrogel system that leverages the cooperative interaction between flavonoids and peptide amphiphile hydrogelators (see Figure 7b). This system is designed to exhibit matching mechanical properties and adequate therapeutic effects for accelerating the healing of chronic wounds. The high-aspect-ratio nanofibrils, guided by hydrogen bonding along the longitudinal axis of the fibers, further intertwine to form self-supporting hydrogel networks via a heat-and-cooling gelation process. The hydrogelators, synthesized to co-assemble with flavonoids that share a similar skeleton and phenolic hydroxyl groups, form a hydrogel that provides enhanced solubility and promotes the bias of angiogenic proteins. This cooperative interaction between the L-type gelator and flavonoids contributes to the superior bio-ability of the hydrogel, facilitating more effective and accelerated healing of chronic wounds [136]. Kusjuriansah et al. utilized the freeze–thaw method to fabricate PVA-based composite hydrogels that are loaded with *citrus hystrix* leaf extract (CHLE). To enhance the hydrogels' antibacterial activity and to control the release of the extract, CS and SA were incorporated into the system. The resulting multi-component hydrogels demonstrated excellent biocompatibility and effective antibacterial properties. The controlled release of the CHLE extract was achieved, with the release rate being adjusted to follow pseudo-Fickian diffusion, ensuring a sustained therapeutic effect over time [137]. Additionally, Naeem et al. pioneered to develop hydroxyethyl cellulose-grafted-2-acrylamido-2-methylpropane sulfonic acid (HEC-g-AMPS) hydrogels for the controlled release of Radix Paeonia Alba-solid dispersion (RPA-SD). This controlled-release hydrogel carrier system featured a porous structure, specifically designed for oral delivery of RPA-SD. The hydrogels exhibited outstanding porosity and biodegradable properties, facilitating the release of the active ingredient within the body. These hydrogels also demonstrated good antioxidant activity, enhancing their potential therapeutic applications [138].

Not only do Chinese herbal medicines have a wide range of sources, but some also exhibit the ability to form preparations while exhibiting pharmacological effects, thereby promoting the integration of medicine and auxiliary treatments. Additionally, some active molecules from TCM can self-assemble to form hydrogel systems. For instance, Wu et al. have devised a self-assembled supramolecular hydrogel consisting of herbal cinnamaldehyde (CA) and FA (see Figure 7c). This biomaterial

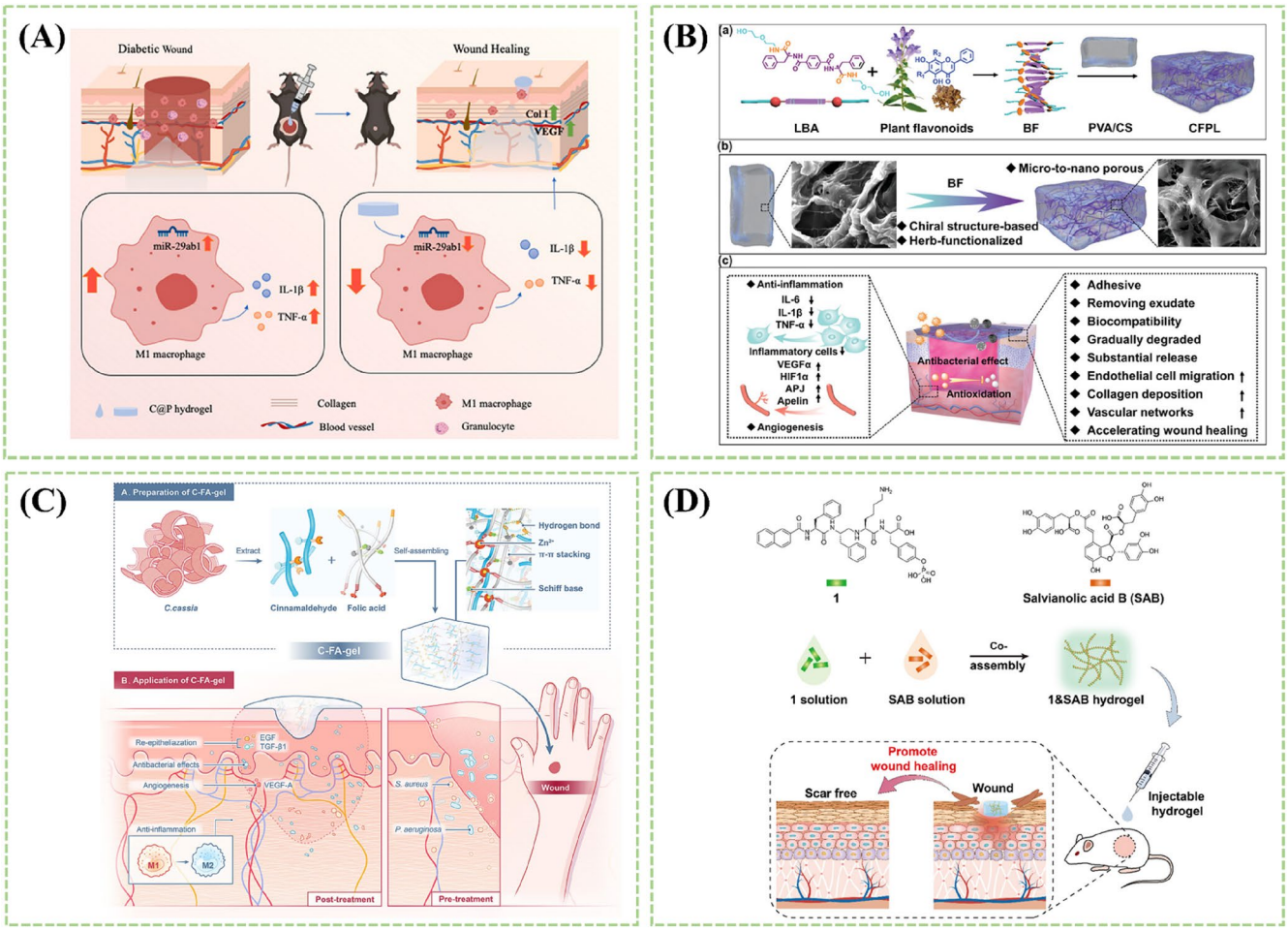

FIGURE 7 | Polymer hydrogels. (A) An injectable and self-healing C@P hydrogel with puerarin for diabetic wound healing and accelerated angiogenesis. Reproduced under terms of the CC-BY license [134]. Copyright 2023, published by Elsevier. (B) A flavonoid-functionalized hydrogel for accelerating chronic wound healing. Reproduced with permission [136]. Copyright 2022, published by John Wiley and Sons/Wiley-VCH. (C) A self-assembled supramolecular hydrogel composed of herbal CA and FA for wound healing [139]. Copyright 2023, published by Elsevier. (D) A two-component supramolecular hydrogel as a potential biomaterial for wound healing. Reproduced under terms of the CC-BY license [140]. Copyright 2023, published by John Wiley and Sons/Wiley-VCH.

displays suitable gelation characteristics due to the synergistic interaction of dynamic Schiff base formation and Zn^{2+} chelation. Specifically, the Schiff base linkages generated between the aldehyde in CA and the amino in FA facilitate the mutual solubilization of CA and FA. Afterward, the C-FA-gel is formed through intermolecular hydrogen bonding, π-π stacking, and Zn^{2+}-mediated cross-linking. The C-FA-gel, as a result, demonstrates robust shear-thinning injectability, self-healing capabilities, and strong tissue adhesion, which allow it to deliver multifunctional effects. The C-FA-gel possesses characteristics including the capacity to decrease inflammation, enhance angiogenesis, and stimulate the regeneration of skin appendages [139]. Moreover, Huang et al. discovered that the co-assembly of SAB (saccharin-6-aminohexanoic acid) with a soluble phosphopeptide leads to the creation of an adhesive and resilient 1&SAB hydrogel (see Figure 7d). This innovative hydrogel, formulated from two small molecules, utilizes the structural element SAB and maintains its inherent functionalities. The process of gel formation is aided by the aromatic-aromatic interactions between the aromatic groups, as well as the establishment of hydrogen bonds. The 1&SAB hydrogel demonstrates high stiffness, strong adhesion, and the capability for rapid release of substances. It also demonstrates notably remarkable antioxidant capabilities, promotes cell migration, aids in vascular regeneration, and reduces scar formation, making it a promising material for tissue engineering and wound healing applications [140]. In addition, Zheng et al. have innovatively reported the self-assembly of rhein into hydrogels through intermolecular π-π interactions and hydrogen bonds, resulting in advanced properties such as excellent stability, sustained release, and reversible stimuli-responsive behavior. This study demonstrated that enhanced cellular uptake allows the rhein hydrogel to accumulate and bind more intensively to the active site of the toll-like receptor, significantly improving anti-neuroinflammatory functions than its free-drug form, with a long-lasting therapeutic effect and almost no cytotoxicity [141]. Besides, Pi et al. synthesized a carrier-free injectable hydrogel, composed of natural small molecules glycyrrhizic acid and norcantharidin (NCTD), which self-assemble via $Cu^{2\pm}$-mediated coordination and hydrogen bonds. This hydrogel can generate ROS, deplete glutathione, and counter hypoxia in the tumor microenvironment via apoptosis, cuproptosis, and anti-inflammation mechanisms. Briefly, the NCTD gel exhibits superior antitumor effectiveness and enhanced biocompatibility compared to free NCTD [142].

4.5 | Conjugated Polymers

Polymer-polymer or polymer-active ingredients conjugates have long been a mainstay in the realm of TCM application, with several effectively transitioned into clinical practice. Attaching a therapeutic agent to a polymer like PEG provides numerous benefits, including increased drug solubility, extended circulation time in the body, a decrease in immune response, managed drug release, and an upgrade in safety. This approach is particularly beneficial in the pharmaceutical field, as it helps to enhance the solubility, stability, and bioavailability of the active ingredients while minimizing their toxicity and immunogenicity [5].

The fusion of two mutually complementary biological active polymer entities by conjugation has genuinely been a popular strategy in drug design. Specifically, Liu et al. developed a novel fluorescently labeled polymer conjugate poly(2,5-bis (Polyethylene glycol oxybutyrate)-1, 4- phenylethynylene-alt-1, 4-phenyleneethynylene, PPE-OB-PEG), for the detection of aristolochic acid (AA). The PPE-OB-PEG polymer exhibits good water solubility due to the presence of hydrophilic linear PEG groups fixed on the side chain of the PPE backbone. Due to the structural compatibility between AA and PPE-OB-PEG, the fluorescence emission of PPE-OB-PEG is markedly attenuated following the introduction of AA, exhibiting an 80% reduction in fluorescence intensity. This response indicates that PPE-OB-PEG was highly sensitive to AA. The system can detect AA within 30 s and has an LOD of 3.00×10^{-8} mol/L, with a satisfactory signal-to-noise ratio ($S/N = 3$) [143]. Besides, Ma et al. have cleverly developed a tumor-specific enhanced oxidative stress polymer conjugate (TSEOP) to amplify the body's antitumor immune response (see Figure 8a). The TSEOP is synthesized through a Passerini reaction involving CA, 4-formylbenzeneboronic acid pinacol ester, and 5-isocyanopent-1-yne. Subsequently, the resulting product is subjected to an azide-alkyne click reaction with PLGA-graft-PEG monomethyl ether to form the final TSEOP conjugate. The TSEOP exhibits amphiphilic properties, has a long blood circulation time, and is stable in vivo. CA and the quinone methide (QM) group can be rapidly generated in response to tumor conditions, inducing strong oxidative stress and immunogenic tumor cell death (ICD). Besides, this cooperative action activates antigen-presenting cells, enhancing the immune response

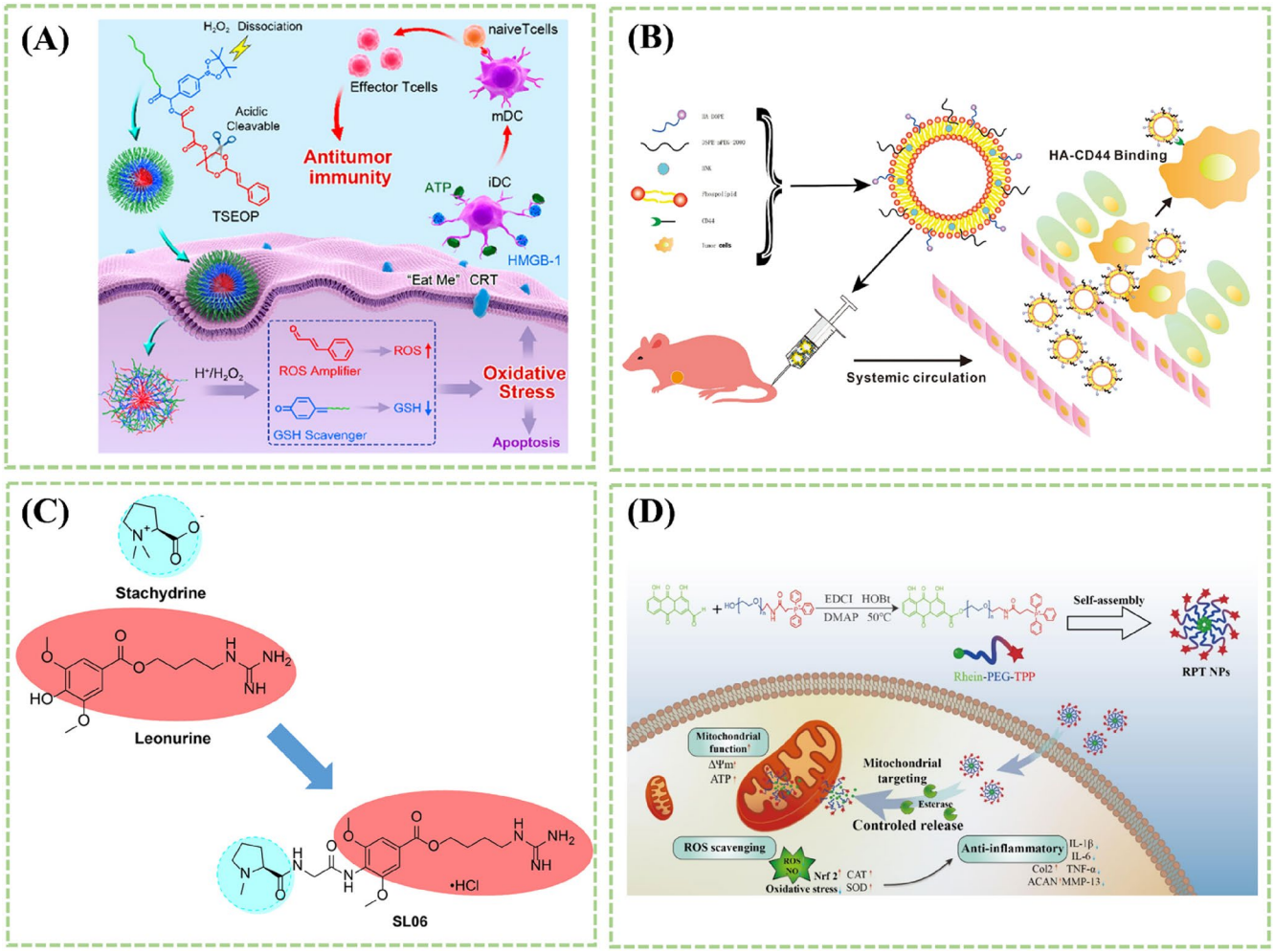

FIGURE 8 | Conjugated Polymers. (A) A tumor-specific enhanced oxidative stress polymer conjugate (TSEOP) for boosting antitumor immunity. Reproduced under terms of the CC-BY license [144]. Copyright 2020, published by American Chemical Society. (B) HNK-encapsulated liposomes being modified with HA-phospholipid conjugates (HA-DOPE) for treating OS. Reproduced under terms of the CC-BY license [145]. Copyright 2022, published by Dove Medical Press Ltd. (C) The conjugates based on the structures of stachydrine and leonurine to treat cerebral ischemic stroke. Reproduced under terms of the CC-BY license [147]. Copyright 2021, published by American Chemical Society. (D) The mitochondrial-targeting and esterase-responsive RPT NPs Nano-Prodrug for the treatment of OA. Reproduced with permission [148]. Copyright 2024, published by Elsevier.

against tumors. The well-tailored structure of TSEOP results in excellent tumor selectivity and superior antitumor efficacy [144]. Furthermore, Zhang et al. have created honokiol-encapsulated liposomes that are modified with HA-phospholipid conjugates (HA-DOPE) for treating osteosarcoma (OS) (see Figure 8b). The HA-DOPE@Lips/HNK system was prepared through a combination of sonication and co-extrusion techniques that ensures a uniform and stable particle size distribution. The modification with HA-DOPE results in a more negative zeta potential due to the presence of carboxyl groups in HA, thereby enhancing the encapsulation efficiency and drug-loading capacity of Lips/HNK. This system exhibits potent biological activities, including inhibition of cell proliferation, induction of apoptosis, arrest of the cell cycle, and disruption of mitochondrial function in OS cells. The HA-DOPE@Lips/HNK complex demonstrates a strong capacity for targeting OS cells, utilizing the binding affinity between HA and CD44, a receptor that is excessively present on the membranes of various cancer cells. This targeting mechanism enhances the delivery of HNK to the tumor site, improving its therapeutic efficacy. Besides, the HA-DOPE@Lips/HNK system demonstrates good biocompatibility, with no apparent damage to major organs [145]. Additionally, Geng et al. fabricated a block copolymer composed of poly(2-(N-oxide-N, N-dimethylamino)ethyl methacrylate) and poly(2-hydroxyethyl methacrylate) (OPDMA-HEMA) to encapsulate and deliver the anticancer agent Cela. The amphiphilic polymer-Cela complex was generated via the spontaneous assembly of the polymers into nanoparticles within aqueous media, a process facilitated by hydrophobic forces and π-π stacking interactions. The resultant nanoparticles led to an enhanced pharmacokinetic characteristic for the drug. The coupling of unbound Cela molecules to the polymers was accomplished by esterifying the carboxyl groups of Cela with the hydroxyl groups of the HEMA block, a critical step since the QM functionality of Cela is vital to its antitumor efficacy. The OPDMA-Cela conjugate exhibited significantly higher drug-loading content, substantial improvement in water solubility, and enhanced blood clearance of Cela molecules compared to free Cela [126]. Xu et al. designed an innovative combined therapeutic approach for renal fibrosis utilizing emodin, which relies on the application of deoxycholic acid-CS coated liposomes (DCS-Lips) and an in situ intestinal gel (IGE) delivery system. The DCS-Lips were fabricated via electrostatic interaction by combining anionic traditional liposomes with cationic deoxycholic acid-CS (DCS), a process that potentially increases the oral bioavailability of EMO. In addition, emodin-loaded in situ colonic gel (EMO-IGE) was prepared by mixing emodin nanosuspensions with plain in situ gel via the cold method for the modification of the gut microbiota. This combined approach, utilizing both DCS-Lips and EMO-IGE, effectively alleviated unilateral ureteral obstruction-induced renal fibrosis in a rat model, demonstrating an innovative and promising therapeutic strategy for renal fibrosis treatment [146].

To further enhance the hydrophilicity and absorption of active ingredients, one effective strategy is to replace the non-covalent interactions between polymers and active ingredients with covalent bonds. This approach results in the creation of a polymer-active ingredients coupler offering several advantages, including providing a more stable and controlled release mechanism, which can be tailored to optimize the therapeutic effect and minimize side effects. For instance, Li et al. have created a range of derivatives by linking the molecular frameworks of stachydrine and leonurine (see Figure 8c). Specifically, the critical intermediate was synthesized through a series of catalytic condensation reactions involving a leonurine derivative, succeeded by additional chemical transformations. Through a screening process, they identified SL06 (06 being the number of the specific conjugate) as having the highest biological activity, including improving neuronal cell survival, inhibiting neuronal apoptosis, and activating superoxide dismutase (SOD) activity in vitro. Additionally, SL06 stimulates the activity of protein kinase B and glycogen synthase kinase 3β and enhances the in vivo expression of the anti-apoptotic protein Bcl-2. Importantly, SL06 also demonstrates the lowest toxicity among the tested conjugates. Furthermore, SL06 can improve neuronal cell viability, increase SOD activity, and decrease the percentage of apoptotic neuronal cells, making it a promising candidate as a potent therapeutic intervention for neuroprotection against ischemic stroke [147]. Huang and colleagues conjugated Rhein with a PEG-modified triphenylphosphonium (TPP) molecule to form TPP-PEG-RH as an esterase-responsive and mitochondria-targeted nanoprodrug (see Figure 8d). The prodrug, in conjunction with the amphipathic polymer, spontaneously self-assembles into Rhein-Phospholipid (RPT) NPs and micelles upon dispersion in aqueous solutions, respectively. The micelles retain their free radical scavenging efficacy unimpaired, while the RPT nanoparticles exhibit improved pharmacokinetics and rapid cellular uptake, preferentially accumulating within the mitochondrial compartment. The TPP-coated exterior of the NPs optimizes their pharmacokinetic properties, aids in effective transport to mitochondria, and boosts cellular internalization, leading to increased deposition within mitochondria and an augmented therapeutic impact in vitro. This drug delivery system effectively delivers Rhein to chondrocyte mitochondria, enhancing the antioxidant properties of Rhein by precisely regulating mitochondrial function. This inhibits the release of pro-inflammatory cytokines and significantly improves the protective activity of Rhein on chondrocytes, representing a novel approach to targeted drug delivery in the treatment of conditions affecting connective tissues [148]. Moreover, Law et al. have designed a drug delivery platform that combines the active ingredient Cela with PVP-co-2-dimethylaminoethyl methacrylate and gold NPs and is further modified by FA. This platform utilizes gold NPs as functional materials due to their favorable properties in cancer drug nanotechnology, such as tunable dimensions, straightforward synthesis, simple modification, and robust optical features that elicit high light absorbance. The polymer acts as a stabilizer to prevent the aggregation of nanoparticles, whereas FA acts as a crucial ligand for the selective targeting and binding to the folate receptor, a protein that is excessively expressed on the exterior of breast cancer cell membranes. This polymer-drug conjugate exhibits high solubility in aqueous mediums and high encapsulation efficiency. Additionally, it demonstrates high efficiency in cellular uptake, and a low colony-forming assay score, and is capable of inducing apoptosis in both 2D and 3D breast cancer model systems [110]. Additionally, Tang et al. designed a solid-phase module for Cycloastragenol (CAG), a pharmaceutical element derived from TCM. They incorporated CAG into oligonucleotides (ON) as an ON-CAG conjugate in a programmable manner using a DNA synthesizer. The 26-base guanine

oligonucleotide, AS1411, was utilized due to its superior targeting capability, strong binding affinity, and minimal immunogenic response. The ON-CAG conjugate demonstrated a similar renoprotective effect as CAG but showed more efficient recovery of the activity of HK-2 cells that were pretreated with cisplatin. It also exhibited higher water solubility, which can be advantageous for drug delivery and formulation. By incorporating a hydrophobic ingredient from TCM into oligonucleotides, the physicochemical properties of CAG were altered, aiding in the identification of novel pharmacological treatments grounded in TCM concepts [149].

4.6 | Other Types of Polymer-Active Ingredient Combination

In addition to the major methods described above, numerous other combination technologies have been developed, which feature distinct personalized characteristics.

Polymer membrane is a straightforward and effective way to deliver drugs. Wu et al. designed an actively targeted drug delivery system intended for the localized therapy of hypertrophic scars (HSs), leveraging the finding that the hypertrophic scar fibroblast (HSF) membrane exhibits an analogous targeting influence. The synthesis procedure included encapsulating quercetin within a diphenyl carbonate crosslinked cyclodextrin metal–organic framework and then overlaying it with an HSF membrane to form the composite. Subsequently, this composite was incorporated into soluble microneedles composed of *Bletilla striata* polysaccharide (BSP), resulting in the formation of the final complex for targeted local delivery. This novel drug delivery system showed superior performance compared to systems that lack HSF modification or the use of microneedles in promoting the efficacy of HS treatment by regulating the Wnt/β-catenin and JAK2/STAT3 pathways and reducing the expression of collagens I and III in HS. Additionally, the prepared microneedles exhibited higher mechanical strength and better physical stability due to the synergistic effect of the BSP matrix. This work confirmed that the fabricated microneedles function by homologously targeting dermal fibroblasts, particularly HSFs, thereby enhancing the therapeutic effect [149]. Besides, Wen et al. selected a polyvinylidene fluoride (PVDF) membrane as the matrix for the immobilization of α-glucosidase. They accomplished this by co-polymerizing tannic acid (TA) with 3-aminopropyltriethoxysilane (APTES) and then subjecting the APTES to hydrolysis. This process led to the formation of hierarchical layer-colloidal nanospheres effectively deposited onto the surface of the PVDF membrane, thereby decorating it. Subsequently, α-glucosidase was immobilized onto the surface via covalent bonding by Schiff base and Michael addition reactions between the residual quinine groups in the coating and the amino groups in the enzyme molecules. The α-glucosidase immobilized on PVDF was then utilized for the identification of potential inhibitors, providing a dependable technique for the detection of enzyme inhibitors from these medicinal sources [150].

Multi-component polymers, as the name suggests, are composed of two or more distinct polymer components that are blended or intermingled to form a cohesive material. This approach allows for the creation of a material that can exhibit properties that are not present in any single component alone. By combining different polymers with complementary properties, it is possible to create a material that possesses a range of characteristics and advantages. In this regard, Xie et al. developed a magnetic polymeric hybrid that mimics the effect of basic and aromatic residues of Organic anion transporters 1, which is responsible for mediating the nephrotoxicity of AAs. This hybrid was designed to enrich aristolochic acid I (AA I) and aristolochic acid II (AA II) from TCM. The authors utilized N, N-dimethyl aminopropyl acrylamide, a cationic monomer, to modify the surface of magnetic nanoparticles through polymerization, thereby enhancing the selectivity for aristolochic acids. The high selectivity and capacity for AA I and AA II demonstrated that the ionizable copolymer could be a promising tool for enhancing the extraction selectivity of these compounds in TCM [151]. Moreover, Tang et al. designed an efficient delivery system for four hydrophilic components from *Salvia miltiorrhiza* and *Carthamus tinctorius*, which are major hydrophilic polyphenols. The presence of catechol groups in these polyphenols allowed for the formation of metal-phenolic networks. Iron(III) chloride hexahydrate was selected as the metal source, and polyvinylpyrrolidone K30 (PVP K30) was used to prevent the aggregation of the coordination polymers and control the particle sizes. Remarkably, all four coordination polymers exhibited significantly enhanced antiatherosclerotic effects [152].

As a drug carrier, polymer microspheres have indeed been extensively utilized in oral drug delivery systems. For instance, Zhang et al. synthesized a variety of Panax notoginseng saponins (PNS)-loaded microspheres, utilizing a biodegradable amphiphilic polymer, mPEG-PLA, as the carrier material. The mPEG-PLA microspheres loaded with PNS were prepared using the emulsification and evaporation methods, yielding microspheres with good sphericity, smooth surface textures, relatively consistent particle sizes, and a minimal degree of particle aggregation or bonding. Biocompatibility analyses revealed that the drug-loaded microspheres were noncytotoxic. Additionally, they exhibited a low hemolysis rate and great anticoagulability, indicating their potential for safe use in intravenous injection preparations and antithrombotic formulations. These microspheres hold significant promise for their anti-inflammatory and antitumor activities [153].

Polymer capsules, with their unique properties and versatility, have a wide range of potential applications across various fields, including medicine, biology, and pharmaceutical science. Zhang et al. prepared a collection of microcapsules (MPs) with GelMA cores and PLGA shells, designed for the controlled and sustained release of *Ginkgo biloba* extract (GBE). The capillary microfluidic technique was utilized to encapsulate GBE into GelMA-PLGA MPs, with the MPs being generated using double-emulsion templates. These MPs exhibited good biocompatibility, hydrophobicity, and nontoxicity, making them suitable for therapeutic applications. The mechanism of action involves the slow release of encapsulated GBE from the solidified MPs during the degradation of the polymer, thereby reducing the required drug dose. Most importantly, the GBE-GelMA-PLGA MPs demonstrated the ability to reduce the deposition of amyloid proteins and improve early cognitive impairment in Alzheimer's disease

(AD) patients, highlighting their potential as a promising treatment for AD [154].

Indeed, to reduce the barrier function of the stratum corneum and improve the effectiveness of transdermal drug delivery, microneedling has gained recognition as a highly effective method for promoting enhanced skin permeation. Specifically, Liu and colleagues developed a ROS-responsive NP consisting of fucoidan and luteolin connected by a ROS-responsive bond, namely FTL@SIN. Thioketal (TK) and Sinomenine (SIN) were co-encapsulated to create a formulation that elicits synergistic anti-inflammatory responses. Following this, the FTL@SIN complex was incorporated into dissolvable microneedles made from high molecular weight Fuc (FTL@SIN MNs) for site-specific application and localized drug delivery. The findings indicated that FTL@SIN MNs effectively mitigated macrophage inflammation and decreased key pro-inflammatory cytokines, simultaneously inducing a shift in the polarization of M1-type macrophages to the M2-type, thereby ameliorating synovial inflammation and promoting cartilage repair, which in turn alleviated synovial inflammation and facilitated the healing process of cartilage. Researchers have noted that fucoidan shows synergistic properties, resulting in improved mechanical robustness and increased physical stability when used in various applications. The heightened levels of ROS within the site-specific inflammatory niche promoted the controlled release of the medication and intensified its concentration at the affected area, thereby improving the treatment's potency against rheumatoid arthritis [155]. Polymer sponges are a type of porous transport structure that is particularly effective for the loading and slow release of active ingredients. For instance, Li et al. proposed a novel formulation for baicalin's delivery, which involved combining baicalin with polymer microsponges (BMs). The baicalin BMs were prepared using the quasi-emulsion solvent diffusion method, incorporating a certain amount of polymer ethylcellulose and PVA. This method resulted in the fabrication of spherical and evenly dispersed BMs with a desirable morphology. Notably, the BMs demonstrated the potential to be utilized as slow-release anti-inflammatory agents [156].

The design of a polymer solution loaded with the active ingredients from TCM for wound healing represents a sophisticated approach to harnessing the therapeutic properties of these compounds. Li et al. employed hydroxypropyl methylcellulose (HPMC) and PVP K30 as matrix materials to encapsulate cholesterol myristate (S8) and berberine (BBR), compounds that exert anti-inflammatory and antibacterial properties, respectively. The synthesis yielded a unique film-forming polymer solution termed S8 + BBR FFPS. This solution, in its liquid state, can be atomized onto skin lesions, where it solidifies into a thin film as the solvent dissipates. In detail, HPMC serves as a hydrophilic matrix, facilitating the solubilization of the pharmaceuticals, whereas PVP K30 acts as a binding agent to modulate the drug release, thereby extending the duration of the drug's retention on the skin wound surface. The dual role of these components enhances the concurrent effectiveness of the drugs. This research is pioneering in suggesting the amalgamation of these two monomers, offering promising pharmaceutical options for the clinical management of chronic dermatological conditions, including pressure sores [157].

5 | Challenges and Prospects

The integration of polymers with active ingredients from TCM is a promising approach to address the challenges associated with the detection, extraction, stability, toxicity, solubility, and bioavailability of these compounds. The use of polymers as sensors, carriers, or stabilizers can significantly enhance the therapeutic potential of active ingredients from TCM. Despite the encouraging research results, the field still faces several challenges, and it is imperative to advance the innovation of technologies or strategies to broaden the clinical application potential:

1. Active ingredients loading optimization. The loading rate of the active molecules onto the polymer should be optimized to maintain the stability of the carrier and the desired release profile of the effective ingredients. Besides, the encapsulation technique can also significantly impact the loading process. Most importantly, the incorporation of controlled release mechanisms, such as pH-responsive or temperature-responsive polymer coatings, is expected to be studied in-depth, which can help regulate active ingredient release in a personalized way and maintain therapeutic levels over an extended period.

2. Preparation process simplification. Some complicated or time-consuming traditional methods should be replaced by advanced ones. These processes involve polymer synthesis, active ingredient loading, carrier molding, etc. One-step processes and scalable synthesis are expected eagerly whenever possible, and the standardization of equipment and streamlined quality control should be strictly established.

3. Targeting capabilities enhancement. It is important to develop advanced drug delivery systems that incorporate targeting ligands, such as antibodies, peptides, or aptamers, which can specifically bind to receptors on target cells. Besides, it is also needed to continue with polymer structures engineering to enhance their targeting properties, such as using nanoparticles with a specific surface charge or shape that can interact with biological fluids and target tissues [158]. Capitalizing on the responsiveness of smart polymers to targeted stimuli, active ingredients can be encapsulated and discharged as needed, thereby constructing an intelligent delivery system.

4. Biocompatibility and safety strengthening. For clinical integration, it is necessary to conduct thorough toxicological evaluations to identify any potential adverse reactions and refine the polymer design to minimize risks. It is also important to investigate the pharmacokinetics of polymers to understand their absorption, distribution, metabolism, and excretion in the body, which can help optimize the polymer design for safety. Clinical trials to further evaluate the safety and biocompatibility of polymer-based drug delivery systems are also needed. Furthermore, biodegradable polymers are of significant interest due to their ability to self-degrade within the human body and in natural settings, resulting in less toxic byproducts, minimizing immune and inflammatory responses, and ensuring higher safety profiles. The controlled degradation process is particularly

advantageous for the precise loading and release of active ingredients.

5. Material stability improvement. Optimizing the formulation of the polymer carrier is highly demanded to enhance its stability, including the use of stabilizers, antioxidants, or controlled release mechanisms. It is also critical to store the polymer carriers under optimal conditions like suitable temperature, light, and humidity, to minimize degradation.

6 | Conclusion

The integration of polymers with the active ingredients from TCM represents a significant advance in the field, offering a range of benefits that align with the principles of modern medicine and personalized treatment. With the rapid advancements in materials science, new polymer materials are emerging that exhibit improved biocompatibility, biodegradability, targeting, and stability, which are crucial for the application of polymers in TCM. By optimizing the production process, researchers can enhance the efficiency of separation and extraction procedures, reduce costs, and increase drug-loading capacity. This not only improves the economic viability of the systems but also allows for the development of more potent and effective treatments. The support of policies and the growing market demand for the modernization of TCM further underscores the significance of polymer applications in this field. As the interest in TCM continues to grow, so does the investment in research and development, the discovery of new polymers can be expected which can revolutionize the way for TCM applications. In summary, the application prospects of polymers in active ingredients from TCM are indeed vast. The combination of cutting-edge materials science, nanotechnology, and biotechnology with the rich tradition of TCM holds the promise of transforming TCM into modern, evidence-based, and personalized treatments. This integration is expected to play a pivotal role in the ongoing modernization and precision of TCM, ultimately benefiting patients around the world.

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