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REVIEW

Microcarriers: A Transformative Platform for Advanced Drug Delivery

Chenchen Zhou[1,2] | Hanna Kim[1,2] | Jun Hao Mo[1,2] | Jia Zheng Wong[1,2] | Zihao Guo[3] | Ruiyan Ni[4] | Pyungsub Kim[5] | Mohammed Shahrudin Ibrahim[1,2] | Muhammad Faathin bin Abdullah[1,2] | Soon Min Kwon[1,2] | Xiaojing Zhang[6] | Nam-Joon Cho[1,2]

[1]School of Materials Science and Engineering, Nanyang Technological University, Singapore, Singapore | [2]Centre for Cross Economy, Nanyang Technological University, Singapore, Singapore | [3]School of Electrical and Electronic Engineering, Nanyang Technological University, Singapore, Singapore | [4]Shanghai Frontiers Science Center of Advanced Textiles, Donghua University, Shanghai, China | [5]Department of Chemical and Biomolecular Engineering, National University of Singapore, Singapore, Singapore | [6]Beijing Key Laboratory for Powder Technology Research and Development, School of Aeronautic Science and Engineering, Beihang University, Beijing, China

Correspondence: Nam-Joon Cho (njcho@ntu.edu.sg)

Received: 4 January 2026 | **Revised:** 22 April 2026 | **Accepted:** 30 April 2026

Keywords: drug delivery | microcarriers | polysaccharides | protein | sporopollenin exine capsules

ABSTRACT

Microcarriers have emerged as a promising technology in modern drug delivery. They offer significant advantages in controlled and targeted release of therapeutic agents, providing higher encapsulation efficiency, structural protection, and precise administration. Furthermore, it is vital in ensuring the safety and quality of the active pharmaceutical ingredient during drug delivery as external environmental perturbations may cause premature degradation. With the abundance of naturally derived materials, recent advances in microcarrier fabrication focus on the extraction of natural resources and present various microcarrier designs with improved biocompatibility and functionalization, offering new avenues for the development of versatile drug carriers. This review explores the four principal categories of microcarriers: polysaccharide-based, protein-based, pollen-derived, and other synthetic polymer microcarriers, highlighting their development history, physicochemical properties, and transformative potential for stimuli-responsive release mechanisms.

1 | Introduction

Over the past few years, the global community has experienced firsthand the profound impacts of unpreparedness in the face of unexpected public health crises. However, not long after the World Health Organization officially declared the end of the COVID-19 pandemic in 2023, concerns about the emergence of a second pandemic have resurfaced. This renewed apprehension is fueled by new epidemics that have begun to break out simultaneously and globally again, such as the spread of novel COVID-19 variants, the KP.1 and KP.2 strains (FLiRT) in the United States and Europe, and human metapneumovirus in China [1]. As pandemics appear to be following a recurring pattern, signaling a normalization of the abnormal, biopharmaceutical technologies are evolving beyond the traditional realm of healthcare to become critical to global stability and economic competitiveness [2]. Now recognized as a core national strategic asset in "new security" worldwide, these advanced biotechnologies underscore the urgent need for further research and development, not only to prepare for potential future pandemics but also to tackle

Chenchen Zhou, Hanna Kim, Jun Hao Mo, and Jia Zheng Wong contributed equally to this work.

persistent, long-standing chronic diseases and to maximize the therapeutic efficacy by pursuing optimal solutions like "Drug Delivery System (DDS)" for these public health challenges.

Conventional therapeutic approaches involve systemic side effects caused by their characteristics of non-specific biodistribution, uncontrolled release, and high dose [3]. In this global transition toward a bio-revolution at both socio-political and industrial contexts, "Microcarriers" have emerged as a cutting-edge platform in the domain of drug delivery, offering more efficient, safe, and optimized solutions to overcome the inherent limitations of conventional approaches. By regulating the dosage, timing, and drug release at the target site, a new DDS with microcarriers ensures both efficacy and safety while overcoming barriers to achieving the therapeutic goal [3].

Microcarriers are commonly defined as small particles extensively experimented with and manufactured from distinct core materials, with each portraying unique characteristics such as densities, diameters, and surface charges. With a micro-level particle size, the microcarriers function as a subminiature vehicle for therapeutic agents, facilitating controlled and targeted drug delivery [4]. The emergence of microcarrier technology has bestowed opportunities in exploiting microcarriers' adaptive ability for therapeutic applications, such as tissue engineering [5–7], cell therapy [8–11], and drug delivery [12–15]. In tissue engineering, microcarriers are employed to amplify cells and effectively maintain cell-specific phenotypes, with the application of microcarriers with tissue-engineered scaffolds in repairing and restoring damaged or degenerated tissue [5]; on the contrary, cell therapy focuses on utilizing the cross-linked porous structure of the microcarriers to grow, expand, and harvest stem cells [4]. DDS is defined as a technological formulation or a tool that allows the transportation and introduction of a therapeutic substance within the body [16]. The dawning of drug delivery technology commenced in 1952, with the advent of the Spansule sustained-release capsule technology by Smith, Kline & French Laboratories, allowing a drug release profile of dextroamphetamine sulfate up to 12 h after oral administration [17]. Since then, the evolution and enhancement of drug delivery technologies have skyrocketed, filled with innovation aiming to address clinical challenges by implementing different ranges of drug release windows. However, these are only the tip of the iceberg of technologies, as Mother Nature has provided us with abundant natural resources, waiting to be utilized, or better yet, discovered.

The spellbinding ability of microcarriers to encapsulate drugs has sparked a surge of interest in scientific studies related to microcarrier design, aiming to provide protection by encapsulating therapeutic drugs within the microcarrier, shielding the active pharmaceutical ingredients (API) from external source-dependent premature degradation. The conservation of the API's half-life leads to enhanced bioavailability, potentially increasing efficacy and mitigating systemic side effects, which represents a promising strategy in modern medicine [18]. Furthermore, microcarriers can be engineered to exhibit biocompatibility, biodegradability, and controlled drug release kinetics, enabling tailored therapeutic outcomes [19]. Moreover, the surface of microcarriers can be functionalized with excipients, ligands, antibodies, or other targeting moieties, enabling precise delivery to specific cellular or tissue targets like malignant tumors or inflamed sites [20, 21]. Current technologies are heavily focused on smart microcarriers, where microcarriers can be engineered to become stimuli-responsive, which activates their drug-release mechanism in response to specific environmental perturbations such as temperature changes, pH variations, and enzymatic activity [20, 21].

The first microcarrier, diethylaminoethyl (DEAE)-Sephadex 150, a cross-linked DEAE-dextran, was invented by Van Wezel in 1967 to support the proliferation of anchorage-dependent cells in the large-scale cultivation of animal cells [22]. This innovative foundation laid in the 1960s has cascaded the therapeutic landscape to evolve gradually, from utilizing small-molecule drugs to discovering and creating a new generation of microcarrier therapeutics made from materials like polysaccharides, protein, sporopollenin exine capsule (SEC), and synthetic polymers. With the advancement of technology, the fabrication methods of microcarriers have gradually improved over time to overcome drug delivery limitations, to achieve sustained/controlled drug release and targeted delivery in the body [23–25].

There are many reviews on microcarriers published to date, most of which focus on the application of microcarriers in cell culture. These reviews usually discuss the clinical application of microcarriers in regenerative therapies, such as enhancing cell culture techniques to facilitate large-scale cell expansion [26], application of microcarriers in mesenchymal stem cell cultures for a 3D environment that promotes cell proliferation [27], and potential development of thermoresponsive microcarriers for enzyme-free cell harvesting [28]. Other reviews focus on introducing microcarriers in tissue engineering, exploring their application in cell adhesion [29], and the fabrication techniques to be used for tissue regeneration and repair as scaffolds [5, 30, 31]. In contrast, this review first presents a comprehensive aggregation of insights on current knowledge on the microcarriers in the aspect of drug delivery. It discusses the flexibility and adaptability of microcarriers that can be fabricated from a diverse array of materials (Figure 1), which includes natural polysaccharides (e.g., alginate, chitosan, agarose), protein-based materials (e.g., collagen, gelatin, silk fibroin (SF)), plant-derived substances (e.g., pollen), and synthetic polymers (e.g., poly(lactic-co-glycolic acid (PLGA), poly-L-lactic acid (PLLA), gelatin methacryloyl (GelMA)). Harnessing the unique properties of these microcarriers may provide the necessary tools to address unresolved clinical challenges. A primary clinical challenge involves the potential for immunogenicity and localized inflammatory responses induced by the microcarrier material, which frequently leads to premature clearance and reduced therapeutic efficacy [32]. Parallel to these concerns, uncontrolled burst release resulting from insufficient microcarrier mechanical strength induces toxicity and prevents a sustained delivery profile necessary for many chronic treatments [33]. Furthermore, the transition from bench-scale synthesis to good manufacturing practice-compliant manufacturing often introduces issues like prohibitive operational cost and batch-to-batch variability in particle size and drug loading, creating a substantial bottleneck for clinical translation [34]. The following sections will explore different types of microcarrier origins and their essential intrinsic properties, critically contrast their key developments, discuss how they may address current unresolved clinical challenges through their unique properties, and

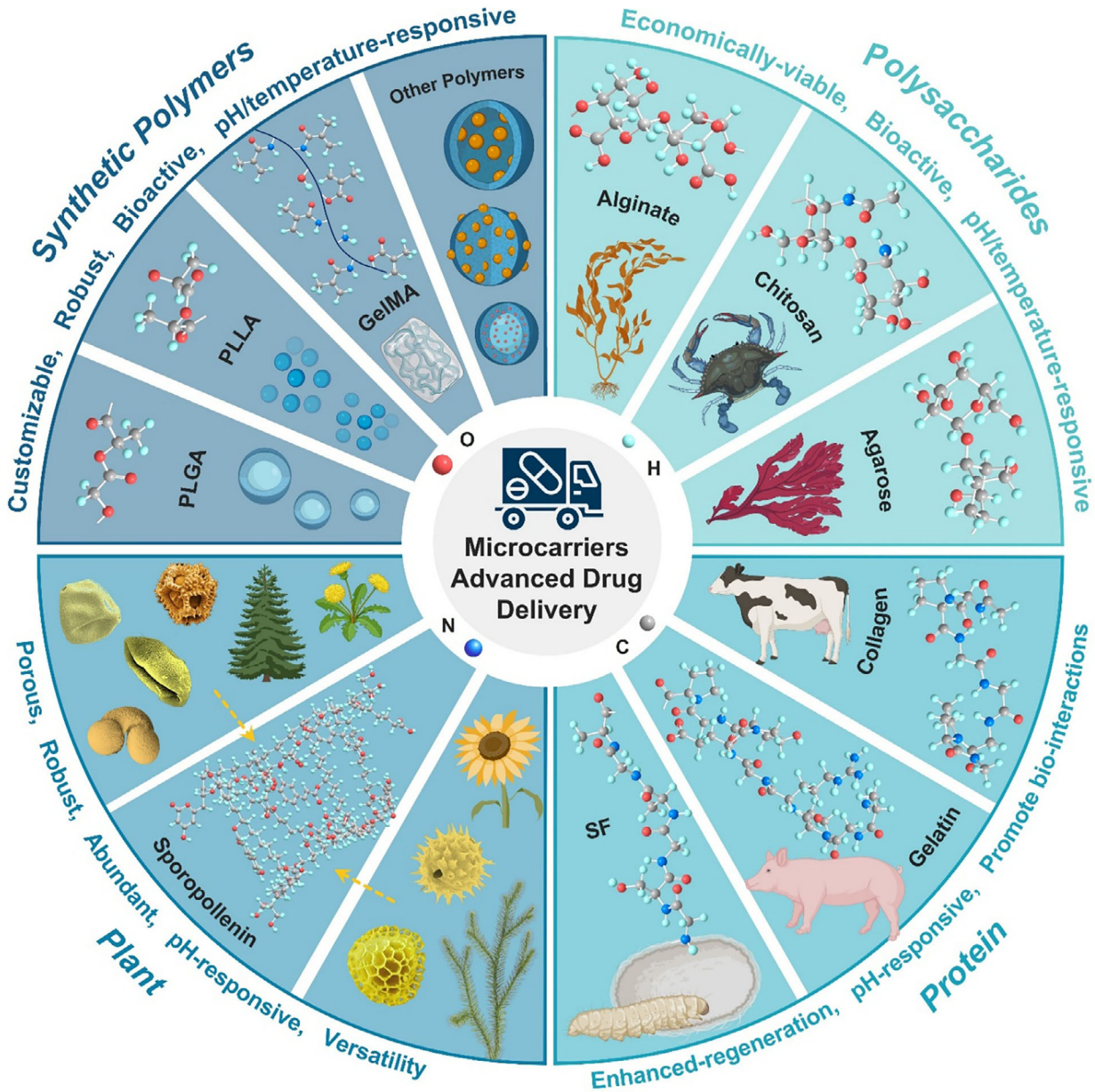

FIGURE 1 | Schematic overview of microcarriers utilized in advanced drug delivery systems (DDS), categorized by their origins and primary material types. Different microcarriers are divided into four major groups: polysaccharides (e.g., alginate, chitosan, agarose), proteins (e.g., collagen, gelatin, silk fibroin (SF)), plant-derived sporopollenin exine capsules (SEC) (e.g., lycopodium SEC, sunflower SEC), and synthetic polymers (e.g., poly(lactic-co-glycolic acid (PLGA), poly-L-lactic acid (PLLA), gelatin methacryloyl (GelMA)). Representative sources and molecular structures are depicted for each type, illustrating the diversity and natural or synthetic origins of materials used to develop microcarriers for targeted and efficient drug delivery applications.

propose possible future research directions for microcarrier-based DDS.

2 | Polysaccharides

Polysaccharides play a pivotal role in microcarrier fabrication due to their tunable physicochemical properties and ability to mimic the extracellular matrix, which collectively enhance cell adhesion, proliferation, and targeted drug delivery efficiency. Polysaccharides, macromolecules composed of monosaccharide units linked by glycosidic bonds, can be sourced from various natural origins, including plants (e.g., pectin, cellulose), animals (e.g., chitosan, glycosaminoglycan), algae (e.g., alginate, carrageenan), and microorganisms (e.g., dextran, xanthan gum) [35]. These biomaterials are not only economically viable due to their easy accessibility but also cost-efficient, and possess key characteristics such as biocompatibility, biodegradability, low immunogenicity, and intrinsic bioactivity. As a result, they have been widely utilized in nanomedicine, tissue engineering, cell culture, and drug delivery applications. In particular, the presence of reactive functional groups, including hydroxyl, amino, and carboxylic acid groups, facilitates straightforward chemical modifications, thereby enhancing

their structural and functional adaptability for a variety of applications [13].

Polysaccharides were first explored in the 1970s as a biodegradable alternative, particularly alginate and dextran for encapsulating therapeutic agents, leveraging their natural abundance and biocompatibility [36, 37]. Traditional polysaccharide-based microcarriers were fabricated through ionic gelation and spray drying by the 1980s [38, 39], which improved drug loading efficiency and release kinetics, leading to the further development of polysaccharide-based drug carriers nowadays [36, 40, 41]. Recent advancements have also explored the use of polysaccharides as natural stabilizers in the fabrication process, enhancing the biocompatibility and stability of microcarriers. For instance, Demina et al. demonstrated the effectiveness of various polysaccharides, such as chitosan and hyaluronic acid, as alternatives to synthetic surfactants for stabilizing polylactide microparticles during fabrication [42]. The polysaccharide encapsulation idea and technique proposed back in the 1980s have shown promising progress and results in the last 5 years. Polysaccharide encapsulation has been shown not only to prolong the release of drugs in different administration conditions, such as different dosage forms like capsules, parenterals, and tablets, but also to facilitate the protection of drugs from light, heat, humidity, or oxygen by preventing decomposition of the drug under these unfavorable conditions [43–45]. This section introduces three widely utilized polysaccharides, alginate, chitosan, and agarose, and exemplifies their applications as microcarriers for drug delivery.

2.1 | Alginate

The anionic hydrophilic polysaccharide, alginate, has gained immense attention due to its inherent properties, low cost, and high availability [20, 46, 47]. It is derived from brown seaweed and composed of a linear chain of (1,4)-linked β-D-mannuronic acid (M blocks) and α-L-guluronic acid (G blocks) (Figure 2a-i), with variable proportions and sequential arrangements [48]. It forms gels through ionic crosslinking in the presence of divalent cations such as Ca^{2+}, thereby allowing for the stable encapsulation of drugs and cells. Because alginate is sensitive to pH, time, and temperature, it enables precise drug release, rendering it especially suitable for controlled and sustained drug delivery applications [46, 49]. In addition, alginate microspheres (MSs) protect drugs from degradation and facilitate targeted delivery, thereby enhancing bioavailability and optimizing drug release profiles, enabling the effective delivery of drugs with poor solubility [46, 49]. Notably, alginate microparticles have been shown to deliver and release anti-inflammatory and antioxidant bioactive drugs such as mesalamine [50], icariin [51], and guar gum succinate [52]. They have enabled effective colon-targeted drug delivery for inflammatory bowel disease (IBD) treatment; pH-responsive, multilayered chitosan–alginate capsule formulations engineered to achieve over 90% colonic drug retention under alkaline conditions and sustained drug release exceeding 24 h [53]. Chitosan and alginate-based multilayer capsules were utilized for the efficient self-loading and sustained release of the anticancer drug, doxorubicin (DOX), with subsequent evaluation of antitumor efficacy through both in vitro and in vivo studies. In a three-group comparative experiment consisting of a control, DOX, and DOX-loaded microcapsules group, the average tumor diameters were monitored over a 3-week therapeutic period (Figure 2b) [54]. The control group exhibited rapid tumor growth, reaching an average diameter of approximately 13 mm by week 3. In contrast, tumors in the free DOX group measured around 9 mm, while those in the DOX-loaded capsule group were further suppressed to approximately 7.5 mm. Despite an identical dosage regimen (2 mg/kg/week), the DOX-loaded capsules resulted in a significantly greater tumor suppression effect, with an inhibition rate of 40.3%, surpassing that of the free DOX group (30.6%) with statistical significance.

Based on the precise modulation of interfacial tension between the ethoxylated trimethylolpropane triacrylate (ETPTA) and SA phases (γ_A and γ_B), Ca-alginate hydrogel microparticles with tunable morphologies were successfully fabricated via Janus emulsion microfluidics (Figure 2c) [55]. When delivered as an enema into the mouse colon, the concave–convex microparticles demonstrated significantly enhanced adhesion and retention compared to the spherical and biconvex counterparts. This improvement is attributed to their bioinspired sucker-like geometry, which increases the contact area and friction with the irregular intestinal mucosa. In vivo fluorescence imaging revealed that the concave–convex hydrogel beads maintained the broadest and most uniform distribution within the colon, indicating their strong potential as long-retention carriers for gastrointestinal (GI) drug delivery applications.

Advanced systems that integrate alginate microcarriers with metal–organic frameworks achieve prolonged drug release [56], while dual crosslinking methods enhance mechanical strength [57], highlighting alginate's versatility in addressing complex therapeutic challenges. The sodium alginate–SF–silver nanoparticle (SA–SF–Ag) MSs exhibited comprehensive functionality as wound dressings, including broad-spectrum antibacterial activity, biocompatibility, sustained silver release, and tissue regeneration capacity. In the Pseudomonas aeruginosa-infected full-thickness wound model (Figure 2d), SA–SF–Ag-treated wounds showed markedly accelerated healing. By day 3, these wounds exhibited notable contraction with minimal exudate, whereas wounds treated with SA-SF dressings without Ag or plain gauze without any silver content retained visible purulent secretions, indicating persistent *Pseudomonas aeruginosa* infection. In contrast, wounds treated with the Ag-impregnated gauze showed an increase in the wound area, suggesting inflammation induced by a high local concentration of silver ions released from the dressing. By day 12, the SA–SF–Ag group achieved the highest wound healing, with a rate of 84.09%, surpassing the other treatment groups [58]. In 2024, Kannan et al. [59] synthesized a hydrogel by crosslinking SA with chitosan using glutaraldehyde and demonstrated sustained release of amoxicillin. The hydrogel also exhibited high absorption capacity for exudates and serum from skin injuries, making it suitable for wound healing applications. In addition to these approaches, further functionalization of alginate microcarriers has enabled more precise control over drug loading and release behavior [60]. For instance, polyethylene glycol (PEG)–sialic acid-functionalized alginate microcarriers, with an optimized particle size of 880 ± 2 μm, demonstrated high drug loading (90%) and encapsulation efficiency (91%), while enabling controlled and prolonged release of curcumin over 72 h, in contrast to the rapid release (<12 h) observed for curcumin in solution. The release mechanism followed Fickian

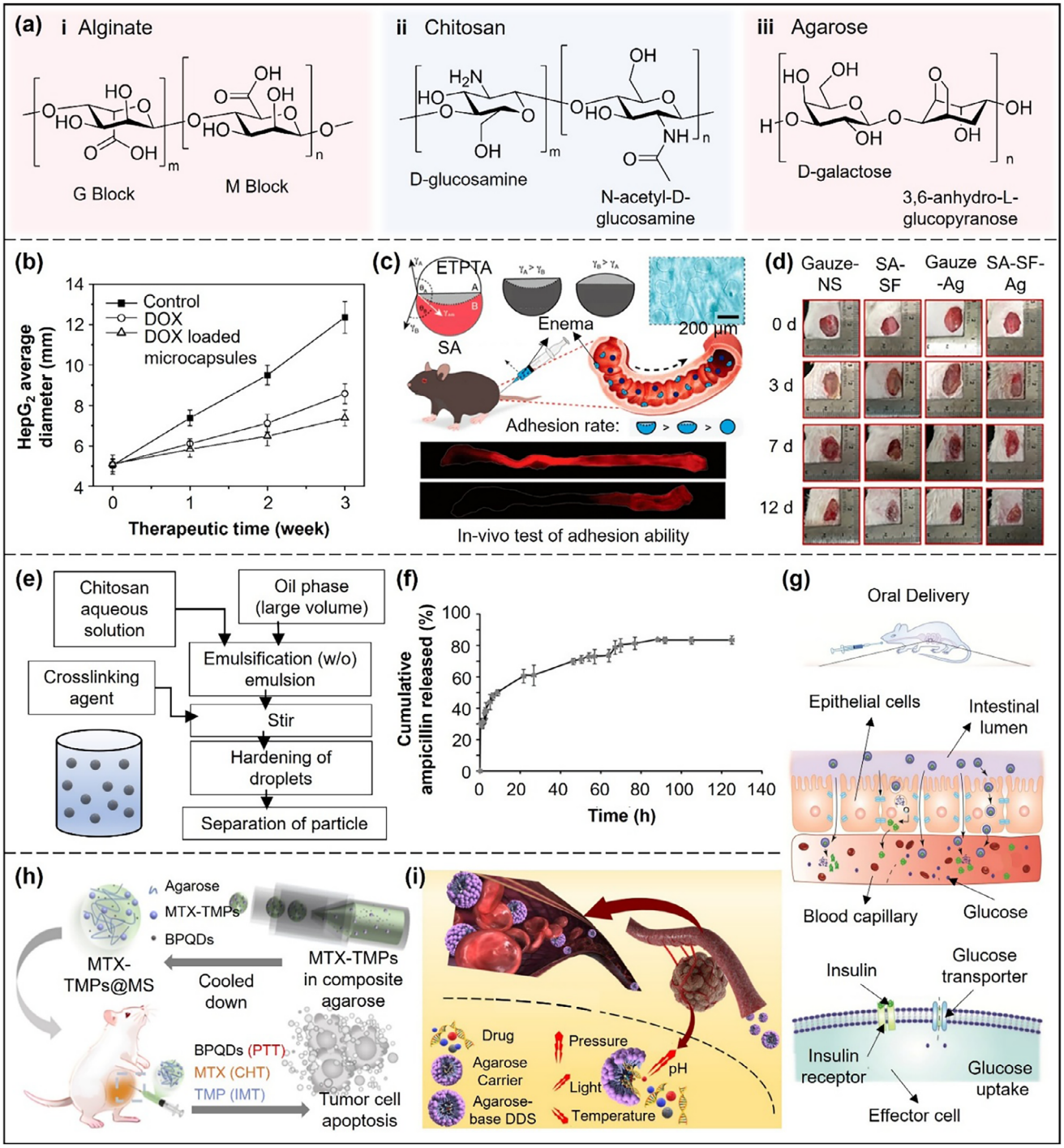

FIGURE 2 | Polysaccharide microcarriers for drug delivery and therapeutic applications. (a) Molecular structure of i. alginate, ii. chitosan, and iii. agarose. (b) Enhanced antitumor efficacy of doxorubicin (DOX) via chitosan–alginate microcapsules (reproduced with permission [54], Copyright 2007, Elsevier). (c) Adhesion performance of shape-controlled Ca-alginate hydrogel microparticles on mouse colon surfaces (ETPTA: ethoxylated trimethylolpropane triacrylate; reproduced with permission [55], Copyright 2024, John Wiley and Sons). (d) Healing efficiency of infected full-thickness skin wounds treated with sodium alginate–silk fibroin–silver nanoparticle (SA-SF-Ag) microspheres (MSs) (NS: normal saline; reproduced with permission [58], Copyright 2024, Sage). (e) Schematic representation of the emulsion cross-linking method for the preparation of chitosan-based microparticles (reproduced with permission [64], Copyright 2004, Elsevier). (f) In vitro release profile of ampicillin from electro-sprayed chitosan micro/nanoparticles showing initial burst followed by sustained release (reproduced with permission [66], Copyright 2008, John Wiley and Sons). (g) Mechanistic representation of chitosan-mediated oral delivery of antidiabetic drugs via mucin interaction and epithelial uptake (reproduced with permission [68], Copyright 2020, Elsevier). (h) Thermoresponsive agarose-based MSs enable near-infrared (NIR)-triggered release of Methotrexate-loaded tumor-cell-derived microparticles (MTX-TMPs) (BPQDs: black phosphorus quantum dots, PTT: photothermal therapy, CHT: chemotherapy, IMT: immunotherapy; reproduced with permission [76], Copyright 2024, Elsevier). (i) Stimuli-responsive drug release mechanism of agarose-based drug delivery system (DDS) triggered by pH, pressure, light, and temperature (reproduced with permission [74], Copyright 2020, Elsevier).

diffusion (n = 0.16) and notably exhibited enhanced drug release under tumor-mimicking acidic conditions (91% at pH 5.5 vs 75% at pH 7.4). These results further highlight the potential of engineered alginate-based systems for targeted anticancer and anti-inflammatory drug delivery applications.

2.2 | Chitosan

Chitosan, derived from the deacetylation of chitin, is a linear polysaccharide composed of β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine units (Figure 2a-ii) [61]. Abundantly sourced from crustacean shells, it is highly regarded for its biocompatibility, biodegradability, and non-toxic nature [62]. Leveraging their hydrophilicity and cationic nature, chitosan hydrogels have shown particularly high efficacy in the delivery of macromolecular compounds, such as peptides, antigens, proteins, oligonucleotides, and genes [63]. Its versatility allows it to be fabricated into micro- and nanoparticles, hydrogels, and films for targeted and sustained drug delivery applications [64–66]. Chitosan's mucoadhesive properties enhance drug retention at target sites [65], and its modifiable chemical structure facilitates advanced delivery performance. The emulsion cross-linking method is a widely used technique for preparing water-in-oil (w/o) chitosan microparticles. This method employs surfactant-stabilized emulsions and a cross-linking agent, such as glutaraldehyde, to solidify chitosan droplets (Figure 2e). It enables control over particle size and morphology and has been effectively used to encapsulate drugs like theophylline, cisplatin, insulin, and 5-fluorouracil. The resulting MSs offer high drug-loading efficiency and tunable release profiles, suitable for both short- and long-term delivery [64]. These attributes have been exemplified in the development of chitosan hydrogel capsules for colon-specific insulin delivery. The capsules protect insulin from enzymatic degradation in the stomach and small intestine, ensuring its release in the colon through microbial degradation. When coated with hydroxypropyl methylcellulose phthalate, these capsules demonstrate stable and targeted insulin absorption in male Wistar rats. Similarly, ampicillin-loaded chitosan micro/nanoparticles demonstrated effective antibacterial activity and a prolonged drug release profile, making them promising candidates for long-term drug delivery via nasal or GI routes. Arya et al. [66] illustrate the in vitro cumulative release profile of ampicillin from chitosan-based micro/nanoparticles over 120 h (Figure 2f). The release pattern is characterized by an initial burst phase within the first 12 h, attributed to the diffusion of surface-associated drug, followed by a sustained release phase due to gradual diffusion through the chitosan matrix. The high encapsulation efficiency (80.4%) and drug loading (50.25%) enabled an extended-release profile, supporting the potential of these particles as a controlled delivery system for prolonged antimicrobial therapy.

In addition, chitosan-based microcarriers exhibit significant potential in cartilage repair. For example, nanocrystal–chitosan particles have been developed to deliver kartogenin, a disease-modifying osteoarthritis drug, directly into the joint cavity [67]. This approach enhances the solubility, stability, and controlled release of the therapeutic agent, highlighting its potential for cartilage regeneration and preclinical applications. Furthermore, chitosan also exhibits therapeutic benefits, including pancreatic β-cell protection, blood glucose reduction, and lipid metabolism improvement. Owing to these properties, it has been extensively applied as a micro- and nanoscale drug delivery carrier for a range of antidiabetic agents such as insulin, glucagon-like peptide-1, exendin-4, and dipeptidyl peptidase-4 inhibitors [68]. Within the GI tract, protonated chitosan electrostatically interacts with negatively charged mucin to form mucoadhesive complexes [68]. These complexes promote drug absorption through vesicular endocytosis and transient opening of epithelial tight junctions, enabling the release of therapeutic payloads into epithelial cells or directly into intestinal capillaries (Figure 2g). This delivery mechanism not only protects peptide drugs from enzymatic degradation but also increases their systemic bioavailability, establishing chitosan as a promising oral carrier for peptide-based antidiabetic therapeutics. In line with these GI delivery mechanisms, hyaluronic acid and cysteine-modified chitosan MSs fabricated via microfluidics demonstrated an encapsulation efficiency of 85.37 ± 1.03% and significantly improved probiotic survival under gastric conditions from 0.20% to 66.90%, enabling controlled intestinal release (34.67%) and cluster of differentiation 44-mediated colon targeting [69]. In a dextran sulfate sodium (DSS)-induced colitis model, these microcarriers enhanced body weight recovery (up to 89.09%) and anti-inflammatory responses, increasing interleukin-10 and short-chain fatty acids (butyric acid up to 5.92 μmol g^{-1}) while attenuating intestinal inflammation.

2.3 | Agarose

Agarose, a polysaccharide derived from red algae, is composed of D-galactose and 3,6-anhydro-L-galactopyranose units linked by α(1,4) and β(1,3) bonds (Figure 2a-iii) [70]. Its gel strength is closely linked to its 3,6-anhydrogalactose content, which directly influences its mechanical properties. Due to its biocompatibility, stability, and thermo-reversible gel-forming nature, eliminating the need for toxic cross-linkers, agarose is highly favored for drug-loading applications [71]. At lower temperatures, agarose undergoes gelation, forming a double-helical, water-insoluble structure that makes it particularly effective in biomedical applications [72]. What sets agarose apart from other polysaccharides is its neutral surface charge across a wide pH range, which minimizes protein corona formation and enhances drug delivery efficiency. Compared to highly charged polysaccharides that face challenges in circulation, agarose offers a more reliable alternative [73]. These unique properties have enabled the use of agarose hydrogels to deliver a wide variety of therapeutic agents, including small molecules, proteins, and antibiotics [74].

Agarose-based microcarriers encapsulate therapeutic agents and undergo structural transformations in vivo, in response to stimuli such as pH variation, light irradiation, mechanical pressure, or temperature fluctuations. These stimuli alter the porosity or swelling behavior of the agarose gel matrix, facilitating the controlled release of the encapsulated drug. Porous chitosan/agarose MSs were developed as carriers for R-phycoerythrin, a protein drug with potential photodynamic therapy applications [75]. Compared to pure chitosan MSs, the incorporation of agarose slightly reduced the loading efficiency but accelerated the sustained release rate, likely due to the relatively loose structure of chitosan–agarose MSs and the fact that agarose cannot chemically crosslink with glutaraldehyde, as evidenced by

the lower loading efficiency values and higher R-phycoerythrin release rates observed in chitosan–agarose MS compared to chitosan MS. The release profile showed a burst increase (<30% in 10 h) followed by a prolonged release over time, indicating the utility of agarose for tuning release kinetics. These findings suggest that agarose enhances diffusion-controlled release behavior, offering an effective strategy for tailoring protein drug delivery in biomedical applications. Moreover, in a recent study, Zhu et al. [76] demonstrate that thermoresponsive agarose-based hydrogel MSs offer a promising platform for immunotherapy in malignant ascites, enabling controlled drug release, immune activation, and selective responsiveness to the tumor microenvironment (Figure 2h). Upon intraperitoneal injection, near-infrared (NIR) irradiation triggers photothermal effects via black phosphorus quantum dots (BPQDs), enabling on-demand release of methotrexate-loaded tumor-cell-derived microparticles (MTX-TMPs). The system combines chemotherapy (CHT), immunotherapy (IMT), and photothermal therapy (PTT), resulting in enhanced tumor cell apoptosis both in vitro and in vivo. The MTX-TMPs utilize homotypic adhesion for targeted drug delivery and modulation of the immunosuppressive tumor microenvironment, indicating strong potential for clinical application in malignant ascites and advanced hepatocellular carcinoma. Besides, Yazdi et al. [74] engineered agarose-based microcarrier DDS with stimuli-responsive drug release, in which physicochemical triggers such as pH variation, thermal changes, light irradiation, and mechanical pressure modulate matrix permeability and the diffusion of encapsulated therapeutic agents. Drugs are encapsulated within agarose carriers, forming a 3D agarose-based DDS and transported via the circulatory system to the pathological site (Figure 2i). Upon exposure to specific stimuli—acidic tumor microenvironment (pH ≈ 6.4), localized hyperthermia (>40°C), photonic energy, or transient pressure, the agarose network undergoes conformational or crosslinking density changes, thereby facilitating controlled release through a combination of Fickian diffusion and network relaxation mechanisms. Such systems significantly enhance site-specific delivery, reduce systemic cytotoxicity, and improve the therapeutic index by aligning drug release kinetics with the pathological microenvironment. In addition to these stimuli-responsive delivery strategies, nanoassembled agarose MSs (NAAMs) have been developed as multifunctional "three-in-one" microcarrier platforms for transarterial chemoembolization, integrating drug delivery, embolization, and multimodal imaging (X-ray/magnetic resonance imaging (MRI)/Raman) [77]. NAAMs enable rapid drug loading (81.49 ± 4.33 mg DOX and 85.66 ± 5.32 mg irinotecan per mL within 30 min; up to 84.84 mg and 88.84 mg at equilibrium) and sustained release over 120 h (DOX: 59.78–74.76%, irinotecan: 81.52–84.62%) via diffusion- and concentration-dependent kinetics. This system maintains high local drug concentration while potentially reducing systemic exposure and enables precise imaging-guided localization (computed tomography/MRI linearity $R^2 = 0.998$), offering improved targeting accuracy for liver cancer and colorectal liver metastases.

3 | Protein-Based Microcarriers

Protein-based carriers are critical in microcarrier fabrication due to their ability to mimic natural extracellular environments, facilitate cell-matrix interactions, and provide a customizable framework for precise drug delivery and tissue engineering applications. Conceptualized and envisioned by Paul Ehrlich during the transition into the 20th century, the theory of "magic bullet" therapy laid a foundation for DDS development, leading to immense research in drug retention time in circulation [78, 79]. Protein-based microcarriers have garnered considerable attention as versatile platforms for drug delivery owing to their inherent biocompatibility, cell compatibility, and tunability for specific therapeutic applications. The 1970–1980s marked a hallmark for protein microcarriers as promising findings were shown, including the first usage of collagen as a drug release system to treat glaucoma in 1973, the first protein recombinant expression of somatostatin at Genentech in 1976, and the first production of recombinant protein insulin in 1982 [79–81]. The incorporation of functional proteins further enables these systems to perform targeted physiological functions, enhancing their potential in precision medicine. Proteins such as collagen, gelatin, and SF confer distinct advantages, including high drug-loading capacity, controlled release kinetics, and low toxicity, positioning them as highly promising candidates for advanced DDS [82]. These carriers can encapsulate a broad spectrum of therapeutic agents, ranging from small molecules to peptides and biologics, while preserving their stability and bioactivity throughout the delivery process [83]. In recent years, protein-based microcarriers have shown promise in addressing drug delivery challenges, treating neurological diseases [84], and facilitating cell therapy [8], owing to their controlled release capabilities [85].

3.1 | Collagen

Collagen, a major structural protein naturally present in the connective tissues of mammals, birds, and fish, has attracted considerable interest as a biomaterial in DDS, owing to its outstanding biocompatibility and biodegradability [86, 87]. The collagen produced through this approach retains its characteristic triple-helical structure (Figure 3a-i), enabling the formation of hydrogels, sponges, and membranes [12, 88, 89]. This structural advantage makes it highly suitable for biomedical applications such as wound healing, cancer therapy, and tissue regeneration. Collagen matrices have been effectively utilized for localized antibiotic delivery, such as gentamicin, demonstrating efficacy in treating infections while promoting wound healing [12]. Furthermore, collagen-based microcarriers feature a 3D matrix capable of stably encapsulating therapeutic agents. By leveraging their inherent biocompatibility and biodegradability, these systems not only regulate drug release but also promote tissue regeneration, thereby enhancing overall therapeutic efficacy [90]. This therapeutic potential is further reinforced through precise control over key parameters such as particle size, degree of chemical crosslinking, and physical processing conditions. These optimizations serve to maximize surface area, mechanical stability, and cellular adhesion and proliferation, ultimately ensuring efficient drug delivery and in vivo safety across a broad range of biomedical applications, including cancer therapy and wound healing.

In this line of research, a representative example is the design of collagen/bacterial cellulose porous MSs, which exhibit excellent dual functionalities as a drug delivery platform by combining high adsorption capacity with sustained release behavior. As demonstrated by Zhang et al. [91], the adsorption kinetics of

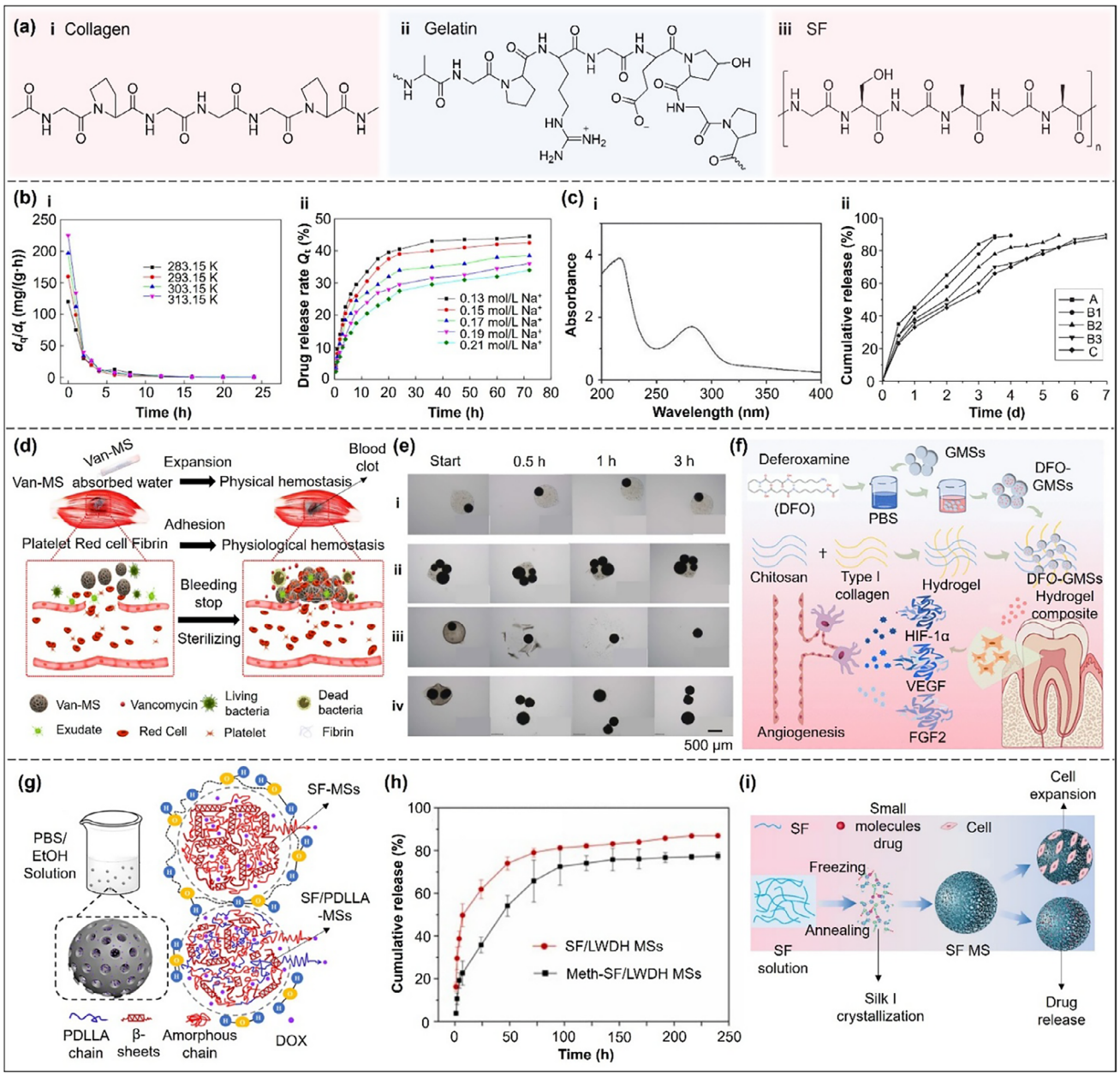

FIGURE 3 | Protein-based microcarriers for drug delivery and regenerative medicine. (a) Molecular structure of i. collagen, ii. gelatin, and iii. SF. (b) i. Bovine serum albumin (BSA) adsorption rate (d_q/d_t) variation versus time on collagen/bacterial cellulose (COL/BC) microspheres (MSs) at different temperatures, ii. BSA release from COL/BC MSs under different Na^+ concentrations (reproduced with permission [91], Copyright 2019, Elsevier). (c) i. UV-Vis spectrum of steroidal saponin (SS)-loaded collagen MSs, ii. Cumulative release profiles of SS from collagen MSs, prepared with different SS:collagen ratios and emulsification times: A (1:1, 40 min), B1 (1:2, 30 min), B2 (1:2, 40 min), B3 (1:2, 50 min), and C (1:3, 40 min) (reproduced with permission [92], Copyright 2022, Taylor & Francis). (d) Schematic illustration of the hemostatic and antibacterial mechanisms of vancomycin-loaded porous gelatin MSs (Van-MS) (reproduced with permission [99], Copyright 2021, Elsevier). (e) pH-responsive dissolution of gelatin–alginate core–shell microparticles: (A,B) in gastric juice (pH 1.32) with single or multiple gelatin capsules, and (C,D) in intestinal juice (pH 7.7) with single or multiple gelatin capsules (reproduced with permission [100], Copyright 2014, John Wiley and Sons). (f) Gelatin-based MS (GMS) hydrogel composite for angiogenic stimulation in dental pulp regeneration (PBS: phosphate-buffered saline, HIF-1α: hypoxia-inducible factor-1 alpha, VEGF: vascular endothelial growth factor, FGF2: fibroblast growth factor 2; reproduced with permission [103], Copyright 2025, American Chemical Society). (g) Mechanism of drug loading and release from SF and SF/Poly(D,L-lactic acid) (SF/PDLLA) MSs based on electrostatic and hydrophobic interactions (EtOH: ethanol, DOX: doxorubicin; reproduced with permission [108], Copyright 2024, American Chemical Society). (h) Cumulative drug release profiles of methanol-treated SF/Liuwei Dihuang (Meth-SF/LWDH) MSs and SF/LWDH MSs in PBS over time (reproduced with permission [110], Copyright 2024, Elsevier). (i) Fabrication and dual functions of SF MSs for drug release and cell expansion (reproduced with permission [112], Copyright 2023, Elsevier).

bovine serum albumin (BSA) onto collagen/bacterial cellulose MSs reveal a rapid initial uptake followed by saturation, well described by the pseudo-second-order model (Figure 3b-i). This suggests that the process is diffusion-controlled and highly predictable. Concurrently, the release profile displays a biphasic pattern, characterized by an early burst release and a subsequent slower phase, with increased ionic strength (higher Na^+ concentrations) modestly reducing the release rate (Figure 3b-ii), likely due to osmotic pressure and electrostatic interactions. These findings underscore the potential of materials for controlled therapeutic delivery in complex physiological environments.

Additionally, Yang et al. [92] demonstrated the successful encapsulation of steroidal saponins (SS) within collagen MSs. The ultraviolet (UV)–visible absorbance spectrum of the SS-loaded collagen MSs (Figure 3c-i) displays a clear peak at 282 nm, aligning with the known maximum absorbance wavelength of pure SS and confirming that the active compound has been successfully incorporated into the collagen MS matrix. Also, the in vitro drug release profile further elucidates the controlled release behavior of the SS-loaded collagen MSs (Figure 3c-ii). Across all formulations, a minimal initial burst (<40%) was observed within the first 12 h, followed by a gradual, sustained release extending over 7 d, ultimately reaching cumulative release rates of up to ≈90%. Notably, formulations with higher collagen content exhibited slower release rates, which is attributed to reduced porosity and more homogeneous drug dispersion within the denser collagen matrix. These observations suggest a diffusion-dominated release mechanism and underscore the potential of collagen MSs as a platform for long-term, controlled delivery of osteoinductive agents. Extending these controlled release strategies, crosslinked collagen-based MSs encapsulating polyvinylpyrrolidone-based aripiprazole solid dispersion have been developed for long-acting intramuscular drug delivery [93]. This system increased aripiprazole solubility by 15-fold, achieved sustained release over 30 days, and enhanced bioavailability by 225% compared to ground microcrystalline aripiprazole. The release mechanism followed the Hixson–Crowell model, indicating surface erosion–controlled drug release, while the solid dispersion enabled amorphous drug formation.

3.2 | Gelatin

Protein-based microcarriers such as gelatin were traditionally fabricated via desolvation and emulsification for microencapsulation, while recent advancements have focused on surface modification to improve cell adhesion and proliferation [94–96]. Gelatin, derived from collagen hydrolysis and typically exhibiting a random coil conformation (Figure 3a-ii), is fully bioresorbable in biological settings and lacks the antigenicity often associated with other proteins [97]. Its non-toxic, non-carcinogenic, and non-immunogenic characteristics make gelatin a highly attractive carrier for controlled drug delivery [94]. Notably, crosslinking gelatin with isophorone diisocyanate improves its solubility, swellability, and biodegradability, thereby facilitating the effective delivery of 5-fluorouracil via anomalous transport mechanisms [98].

The following section outlines the major research trends and achievements in the development of gelatin-based microcarriers.

Cao et al. [99] developed vancomycin-loaded porous gelatin MSs (Van-MS) that exhibit a rapid dual mechanism of hemostasis and antibacterial activity for traumatic soft-tissue wounds (Figure 3d). Upon application, the MSs absorb exudate and swell to form a tight physical seal, which arrests bleeding and concentrates red blood cells, platelets, and fibrin to activate the endogenous coagulation cascade, thereby yielding a stable clot. Concurrently, vancomycin is released in a controlled and sustained manner from the porous matrix, maintaining local concentrations above the minimum bactericidal concentration and continuously sterilizing the wound to eradicate *Staphylococcus aureus* and other pathogens. This integrated design, combining immediate hemostatic efficacy with prolonged antimicrobial delivery, makes Van-MS a promising microcarrier for emergency trauma care, where rapid bleeding control and infection prevention are paramount.

Additionally, Huang et al. [100] demonstrated the pH-responsive degradation behavior of core–shell gelatin–alginate microparticles under simulated GI conditions. Microparticles with single (Figure 3e-i) or multiple (Figure 3e-ii) embedded gelatin capsules maintained their spherical shape for at least 3 h in gastric juice (pH 1.32), confirming that the alginate shell protected the gelatin core from acidic degradation. In contrast, when placed in intestinal juice (pH 7.7), the alginate shell completely degraded within 30 min (Figure 3b-iii,iv), releasing the gelatin core. These results confirm the potential of the microfluidically synthesized gelatin–alginate microparticles as pH-responsive oral drug carriers that protect therapeutic payloads in the stomach and enable triggered release in the intestine.

In a separate study, Nii et al. [101] developed gelatin microparticles via emulsion and chemical or dehydrothermal crosslinking, enabling drug release specifically triggered by collagenase. Gradual degradation of these microparticles in collagenase-rich environments, such as injured or regenerating tissues, enables spatiotemporal control of growth factor and therapeutic delivery, preventing hypoxic cell death while promoting wound healing and physiologically relevant 3D cell culture. The versatility of gelatin was further evidenced in flurbiprofen-loaded solid self-microemulsifying DDS [102], where its use as a solid carrier markedly improved oral bioavailability in rats. Wang et al. [103] developed a DDS by incorporating deferoxamine (DFO)-loaded gelatin-based MSs (GMSs) into a hydrogel matrix to enhance the angiogenic potential of dental pulp stem cells (Figure 3f). DFO is initially dissolved in phosphate-buffered saline (PBS) and loaded into gelatin MSs to form DFO-GMSs, which are then embedded within a chitosan/type I collagen hydrogel to create the final composite. Upon implantation, DFO is gradually released, stabilizing hypoxia-inducible factor-1 alpha (HIF-1α) and upregulating angiogenic factors such as vascular endothelial growth factor and fibroblast growth factor 2, thereby promoting endothelial activation and neovascularization. These results suggest that the composite is a promising biomaterial for vascular regeneration in dental pulp tissue.

3.3 | SF

SF, a natural polymeric protein extracted from silkworm silk, is composed of amino acids such as serine and glycine, held

together by hydrogen and ionic bonds to form a β-folded lamellar structure (Figure 3a-iii) [104]. Owing to its notable biocompatibility, biodegradability, excellent mechanical strength, and strong cell affinity, SF has been widely utilized as a sustained-release carrier for anticancer drugs and protein therapeutics, as well as in wound healing studies to promote tissue regeneration and prevent infections [105, 106]. For instance, SF-based microcarriers have been used to encapsulate and deliver bone morphogenetic proteins, achieving encapsulation efficiencies of 67.9–97.7% and enabling a two-phase release over 14 d [107].

Porous MSs composed of SF and poly(D,L-lactic acid) (PDLLA) enable precise control over drug release rates by modulating internal structure and hydrophilic–hydrophobic interactions (Figure 3g) [108]. Uniform SF/PDLLA composite MSs are obtained through a self-assembly process in a PBS/EtOH co-solvent system. Compared with SF-only MSs composed of dense β-sheets and amorphous chains, the incorporation of PDLLA chains and hydrophobic domains alters packing density and drug–matrix interactions. Drug molecules, such as DOX, are uniformly distributed within the matrix, and their diffusion behavior is regulated by polymer composition and intermolecular forces. This study demonstrates that SF/PDLLA MSs are promising drug carriers with tunable structural stability and sustained release behavior. Furthermore, SF-based microcarriers engineered for advanced cancer therapy exhibit multi-responsive (pH, reactive oxygen species, glutathione, hyperthermia) release profiles [109], releasing more than twice the amount of DOX under acidic (pH 4.5) tumor-mimicking conditions compared with neutral pH 7.4. This efficacy stems from the tunable β-sheet structures of SF, enabling stable drug encapsulation and on-demand release, while further modifications (e.g., folic acid conjugation or transgenic alterations) enhance tumor targeting and therapeutic potency. Similarly, Wang et al. [110] engineered SF MSs loaded with Rehmannia Liuwei Dihuang (LWDH) extract to achieve controlled and prolonged drug release for endothelial protection under hyperglycemic conditions. The cumulative release profile (Figure 3h) reveals that methanol vapor-treated SF/LWDH MSs exhibited an initial burst release of approximately 34.81% within 24 h, whereas untreated SF/LWDH MSs showed a higher burst release of about 61.88%, maintaining a gradual and sustained release over 9 days in PBS. This behavior is attributed to enhanced β-sheet formation (49.16% post-treatment vs 28.86% pre-treatment), which increases matrix crystallinity and densifies the MS structure, thereby restricting drug diffusion. These findings underscore the potential of β-sheet structural tuning in SF MSs as an effective strategy for improving the pharmacokinetics of traditional multi-component herbal drugs. Meanwhile, SF microparticles for intra-articular osteoarthritis delivery exhibit prolonged joint residence and decreased clearance. Sustained intra-articular release of small molecules over several weeks was confirmed, indicating a potentially significant advancement in arthritis therapy [111].

Zhu et al. [112] developed a green, chemistry-independent method for fabricating SF MSs with Silk I crystalline structure, optimized for drug delivery and cell culture applications. The process involves freezing and annealing a SF solution to induce Silk I crystallization and form porous MSs with dual functionality (Figure 3i). These MSs not only provide a stable and biocompatible matrix for sustained drug release (e.g., DOX) but also support mammalian cell adhesion and proliferation due to their interconnected pore structure. Transforming SF solution into crystalline MSs enables small-molecule drug release and cell expansion, while eliminating the need for organic solvents or chemical crosslinkers. This eco-friendly approach offers a versatile platform for multifunctional biomedical applications such as tumor therapy, 3D cell culture, and regenerative medicine. Additionally, Mahaling et al. designed a silk-gelatin hybrid hydrogel as a potential carrier for RNA therapeutics and performed molecular modeling to investigate RNA-polymer interactions in protein-based microcarriers such as collagen and SF. The system showed potential for delivering transfer RNAs (tRNA-ALA, tRNA-GLN, and tRNA-Leu) and/or messenger RNAs (mRNA-GAPDH, mRNA-β actin, and mRNA-Nanog) [113]. Alongside these advances, carboxyl-activated SF microcarriers coated with SA have been utilized for probiotic colony delivery, achieving one-order higher intestinal colonization despite a 100-fold lower dosage (10^4 vs 10^6 enumerating colony-forming units mL^{-1}) and sustained viability up to 36 h [114]. This system integrates gastric protection, mucosal adhesion, and colony formation, leading to enhanced therapeutic efficacy in colitis by reducing inflammatory cytokines, restoring tight junction proteins, and increasing beneficial Firmicutes while decreasing pathogenic Proteobacteria.

4 | SECs

SECs are gaining attention in drug delivery due to their biocompatibility, robust structure, and versatility. Renowned as the "diamond of the plant world", the sporopollenin not only possesses a unique microstructure with a uniform size distribution but also has unyielding resilience to external stimuli due to its inert nature [115, 116]. The inherent properties of sporopollenin can be derived from its chemical structure (Figure 4a) [117]. Sporopollenin is composed primarily of two types of crosslinking bonds, ester and acetal. The interactions of both crosslinking bonds likely explain their exceptional inertness, with ester being relatively stable in an acidic environment and acetal being highly resistant in an alkaline environment. Sporopollenin's low solubility arises from its entwining hydrophobic and hydrophilic monomer units, and its resistance to enzymatic breakdown by living organisms could be attributed to its diverse monomer configurations and linkages. The presence of *p*-coumarate and naringenin functional groups contributes to the intrinsic function of sporopollenin in protecting the reproductive cells from detrimental external stresses [115, 116, 118, 119], such as UV exposure, desiccation, and microbial attack [120]. SEC can provide extraordinary adaptive stability and endurance under mechanical, thermal, biological, and hydrostatic pressures [115, 116, 118, 119], with elastic moduli up to 16 $\pm$ 2.5 GPa and resistance to hydrostatic pressures exceeding 10 GPa [121].

Toxic components in synthetic substances have raised concerns in drug delivery applications due to their potential adverse effects on the human body. This has shifted attention toward safer, less toxic, and more effective alternatives, such as SECs [122]. However, the application of SECs in drug delivery requires them to be biocompatible (allergen-free and non-toxic). To meet this requirement, pollen grains are defatted and subsequently chemically processed to eliminate cytoplasmic residues and allergenic proteins,

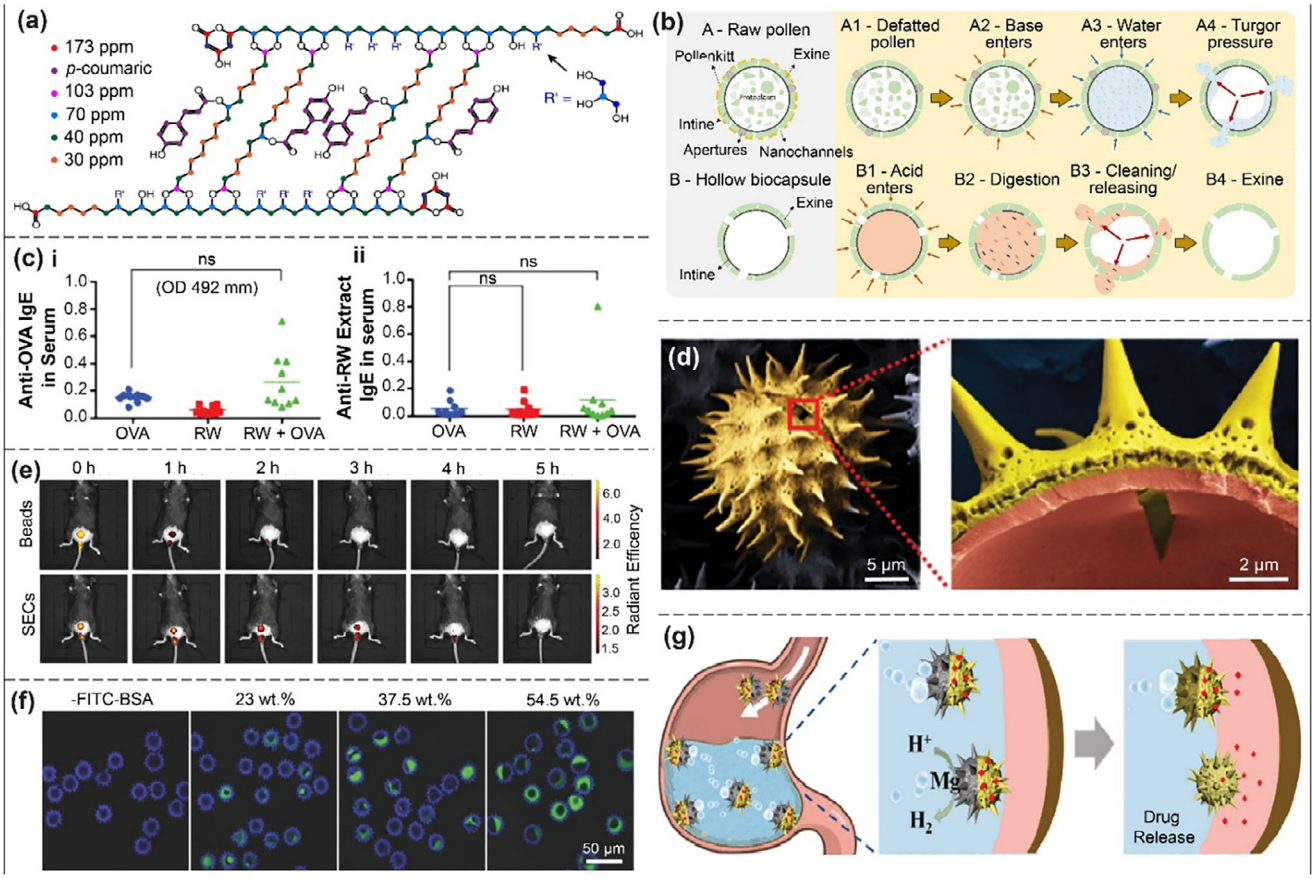

FIGURE 4 | SEC and its applications in targeted and controlled drug delivery. (a) Chemical composition of sporopollenin (reproduced with permission [117], Copyright 2019, Springer Nature). (b) Conventional treatment process to fabricate SEC (reproduced with permission [126], Copyright 2023, Elsevier). (c) Serum immunoglobulin E (IgE) antibody response of mice, following oral immunization with either 100 μg ovalbumin (OVA) alone, 5 mg of ragweed (RW) SEC alone, or a combination of both weekly for 8 weeks. IgE response (i, was measured on day 85; and ii, measured on day 140 with an enzyme-linked immunosorbent assay). For each analysis, samples ($n = 10$) were diluted 1:25 in 0.05% Tween 20 in phosphate-buffered saline (PBS) (reproduced with permission [127], Copyright 2018, Elsevier). (d) Spiky morphology of sunflower pollen taken with SEM (reproduced with permission [136], Copyright 2020, Springer Nature). (e) In vivo living fluorescence imaging of pollen adhesion in the mouse's bladder (reproduced with permission [122], Copyright 2024, John Wiley and Sons). (f) Confocal laser scanning microscopy imaging of fluorescein isothiocyanate-bovine serum albumin (FITC-BSA) loaded sunflower SEC (reproduced with permission [137], Copyright 2017, John Wiley and Sons). (g) sti of magnesium (Mg)-coated pollen micromotors in the stomach (reproduced with permission [138], Copyright 2024, Elsevier).

producing allergen-free microcarriers for biomedical applications (Figure 4b) [115, 123–126]. Ragweed (*Ambrosia elatior*) SECs were evaluated against allergenic ragweed extracts to confirm their allergen-free status. The absence of high immunoglobulin E (IgE) responses suggested that ragweed SECs are unlikely to trigger allergic reactions (Figure 4c) [127]. Moreover, pollen grains have been verified and recognized to be safe for human ingestion by the United States Food and Drug Administration (FDA), and are widely used in supplements and herbal medicines [128]. To assess the biocompatibility of SECs, sunflower (*Helianthus annuus*) SECs were subjected to cell viability and hemolysis assays. The findings showed that the cytotoxicity was classified as class 0 (≥ 95% relative growth rate) and a hemolysis rate of < 5%, indicating that sunflower SECs pose no significant hemolysis risk [122].

SECs provide mechanical stability and protect encapsulated drugs from environmental degradation, while their internal cavity enables efficient drug loading [129, 130]. The mechanical structure of SECs originates from their biological function, in which pollen grains protect the genetic materials against unfavorable environmental conditions such as elevated temperature, UV radiation, prolonged desiccation, etc [126, 128]. The efficacy of SECs in drug delivery stems from two distinct characteristics: (i) apertures, large surface pores (diameter of ≈1–2 μm), and (ii) omnidirectional nanoscale channels, facilitating efficient drug encapsulation and release [126]. Furthermore, the versatility of SEC emanates from the fact that pollen is an infinite and abundant natural material [131]. Pollen is also readily accessible, cost-effective, and can be processed on an industrial scale [132]. However, only a limited number of pollen species have been explored for the fabrication of SEC, yet there are ≈310 000 recorded plant species reproduced through pollination, each having unique morphological characteristics, offering significant potential for customizable drug delivery [127]. Among the varying pollen SECs for drug delivery applications, Sunflower and Lycopodium (*Lycopodium clavatum*) pollen species are the most extensively studied. Other pollen species, such as European hazelnut (*Corylus avellana*) and silver birch (*Betula pendula*),

have been explored for the fabrication of SEC, and reported to have varying drug encapsulation and release profiles for tailored DDS, as shown in Table 1 [133, 134].

4.1 | Sunflower SECs

Sunflower pollen has garnered attention as a promising pollen species for the fabrication of SEC due to its distinctive morphology. The pollen grains feature a spiky exterior surface, a tripartite structure, and a uniform size distribution of 29.74 ± 0.11 μm (Figure 4d) [129, 135, 136]. The unique morphology of sunflower SEC effectively addressed the limitations associated with traditional intravesical instillation treatments, such as short drug retention times and inadequate bladder contact. This morphology enhances adhesion to the bladder lining, remains stable after multiple urinations, and significantly shortens the instillation-maintenance duration from 1–2 h to ≈20 min. Furthermore, drugs encapsulated within SECs exhibit sustained elevated concentrations in the bladder for up to 5 h compared to those without SECs (Figure 4e) [122]. Additionally, to enhance the functionality of SECs, sunflower SECs coated with enteric coatings have been successfully used for the oral delivery of BSA, protecting it in simulated gastric fluids (SGF) and enabling its release in simulated intestinal fluids (SIF), providing targeted and controlled drug release (Figure 4f) [128, 137].

Sunflower SECs have also been innovatively transformed into microrobots by coating one side of the SECs with heavy metal to facilitate self-propulsion via the formation of H_2 bubbles caused by the reaction of heavy metals with internal human fluids. For instance, magnesium-coated SECs react with the acidic gastric fluids to generate H_2 bubbles, propelling the SECs to the gastric lining for targeted drug delivery (Figure 4g). Coupled with the adhesive properties of sunflower SECs, this mechanism allows for controlled and sustained drug release in the GI tract [138].

4.2 | Lycopodium SECs

Lycopodium pollen is a promising and widely studied species utilized for the fabrication of SECs, which show extreme resistance to chemical degradation [139, 140]. Lycopodium has a unique morphology that includes a reticulate-patterned structure with trilete (Y-shaped) scars on the surface (Figure 5a) [141]. The pollen is also characterized by large inner cavities, along with numerous, narrow, and omnidirectional channels facilitating the flow of fluids into and out of the pollen's interior [125, 142]. The unique functions of lycopodium SECs were reported to encapsulate ibuprofen with 97% efficiency and show non-toxicity, taste masking, targeted intestinal release, and stability in gastric fluid (Figure 5b) [123]. SECs have also been used for vaccine delivery. For example, Atwe et al. reported the feasibility of using *Lycopodium clavatum* spores for oral vaccination, where *Lycopodium* SEC encapsulated ovalbumin (OVA) was introduced as a model antigen on mice, inducing a stronger OVA-specific immunoglobulin G (IgG) and immunoglobulin A (IgA) immune responses for a prolonged period up to 7 months, demonstrating potential as a novel vaccination system (Figure 5c) [124]. The superiority of SECs in oral vaccination stems from their capacity to protect the vaccine against the harsh acidic and enzymatic environment of the GI tract [126, 127]. Additionally, lycopodium SECs have demonstrated effective photoprotection, preventing protein denaturation and thereby enhancing bioavailability. Folic acid (Vitamin B_9)-loaded SECs show unchanged adsorption spectra after 4 and 6 h of sunlight exposure, demonstrating the ability of SEC to protect drugs against UV-induced degradation. The photoprotection capability is attributed to its phenolic phenylpropanoid moieties within sporopollenin, which endure even after rigorous chemical treatments (Figure 5d) [14].

4.3 | Other Pollen Species

Although less common, several other pollen species have also been investigated. For example, European hazelnut, silver birch, ragweed, date palm (*Phoenix dactylifera L.*), and dandelion (*Taraxacum officinale*) exhibit promising potential for drug delivery applications due to their unique morphology, robust structural properties, high encapsulation efficiency, and drug loading capabilities [127, 133, 134, 143, 144]. For example, ragweed SECs have been utilized in oral vaccine delivery. These SECs were encapsulated with OVA, demonstrating a strong and lasting OVA-induced robust mucosal and systemic immune response, persisting for approximately 3 months post-vaccination in vivo [127]. In cancer treatment, silver birch SECs have shown promising results as well (Figure 5e). Imatinib mesylate-loaded SECs demonstrated significant anti-proliferative activity against the WiDr human colon carcinoma cell line in MTT assay, with treatment durations of 24 and 48 h using imatinib mesylate-loaded SECs with concentrations ranging from 10–1000 μg mL^{-1}. These examples highlight the potential of exploiting various pollen SECs with unique features and morphologies in DDS [133]. However, a drawback of using SECs for drug delivery lies in their internal cavity and porosity, which are ambivalent in nature, facilitating both drug encapsulation and the ingress of gastric fluids, ultimately leading to the denaturation of the encapsulated proteins. To mitigate this, polymeric coatings have been employed to protect the pollen-encapsulated proteins from gastric fluid-induced degradation before reaching the GI tract (Figure 5f) [145]. For example, SECs were coated with Eudragit (EUD) for controlled drug release. Studies have confirmed that uncoated SECs have a faster drug release rate compared to SEC-coated EUD in both SGF (pH 1.2) and SIF (pH ≈ 7), with uncoated SECs having a ≈34% release within 30 min in SGF as compared to coated SECs at ≈25%. SEC-coated EUD exhibits potential for targeted and controlled drug delivery, particularly for the treatment of GI cancer, by controlling the drug release rates within the GI tract [146].

5 | Synthetic Polymer-Based Microcarriers

In addition to naturally derived polysaccharides, proteins, and SECs, synthetic polymer-based microcarriers have garnered increasing attention as next-generation platforms in biomedical engineering. These carriers, comprising materials such as PLGA, PLLA, and GelMA, are valued for their precisely tunable physicochemical properties, reproducible fabrication methods, and robust mechanical integrity. In the early 1960s, the biodegradable synthetic polymer PLGA was identified as surgical sutures and monofilaments [157]. Up until the 1980s, the utilization

TABLE 1 | Compilation of existing SECs for controlled drug delivery applications.

Pollen	Characteristics	Drug	Loading	Release	Target problem	Year[Ref.]
Lycopodium	Uniform size, narrow omnidirectional channels, taste masking, targeted release	Ibuprofen	97 ± 1%	45 min, 88 ± 1% in SGF; 5 min, 85 ± 2% in SIF	Anti-inflammatory	2013 [123]
Lycopodium	Porous, large (≈tens of micrometers in diameter), targeted oral vaccine delivery, intestinal tissue adhesion	OVA	N.A.	Sustained OVA-specific IgG and IgA antibodies ≤ 7 months	Immune response	2014 [124]
Lycopodium	Hollow, consistent diameter (25 μm), omni-directional nanochannels (200–300 nm), pH-dependent released, bioavailability	3,4-diaminopyridine	10.1% with 3,4-diaminopyridine/50% SEC/39.9% shellac	8 h, 72.2 ± 4% retained in SGF; 8 h, ≈60% in SIF	Botulinum neurotoxin A intoxication	2016 [125]
Date palm	20.3 ± 0.1 μm in length, 10.5 ± 0.1 μm in breadth, macropore surface, biocompatible	Ibuprofen	97.20% at pH 6.0 for 5 h at room temperature	Chitosan-glutaraldehyde based polymer-coated SEC: maximum release, ≈47% in SGF, 8 h, 94.20% in SIF	Anti-inflammatory	2016 [143]
European hazelnut	Hollow, open apertures	Pantoprazole	29.81%, passive	1 h, 60.84 ± 0.31% in SIF	Duodenal ulcer, gastric ulcers, gastroesophageal reflux disease	2017 [134]
Sunflower	Uniform size, hollow, spiky surface	BSA	42.2 ± 4.8%, vacuum	Uncoated SEC: 15 min, ≈90%, 60 min, 100% in both SGF and SIF; EUD L100-coated SEC: 2 h in SGF and 4 h in SIF, 2.6 ± 1.2%, 8 h in SIF, 31.3 ± 1.9%, 30 h, 54.2 ± 9.7% in SIF	N.A.	2017 [137]
London plane tree (*Platanus orientalis)*	Intact, highly reticulated and porous surface, thermally stable	Paracetamol	8.2%, passive; 23.7%, evaporation	Passive-loaded SEC: 15 min, 31.2 ± 3.6% in SGF; 24 h, 56.0 ± 1.9% in SIF; Evaporation-loaded SEC: 5 min, 22.5 ± 0.2%, 120 h, 29.2 ± 0.6% – 33.2 ± 0.2% in SGF; 5 min, 21.9 ± 0.3%, 120 h, 26.3 ± 0.2% – 39.5 ± 0.1% in SIF	Analgesic	2017 [147]

(Continues)

TABLE 1 | (Continued)

Pollen	Characteristics	Drug	Loading	Release	Target problem	Year[Ref.]
Pine	Micron sized (45–75 μm) tripartite structure, 2 air sacs attached on a sporoplasmic central cavity, high drug loading	BSA	26.5 ± 3.7% via vacuum loading for hydrochloric acid-treated SECs with additional trypsin treatment	N.A.	N.A.	2017 [148]
Silver birch	Triangular shape, three apertures, uniform size (≈25 μm), anti-proliferative	Imatinib mesylate	21.46%, passive	120 h, 100% in SGF; 24 h, ≈65% in SIF	Cancer treatment	2017 [133]
Dandelion	Cage-like structure with long spines, uniform size (≈23–27 μm), high drug loading	BSA	53.72 ± 0.54%, vacuum	N.A.	N.A.	2018 [144]
Ragweed	Hollow, spherical (15-18 μm in diameter), short spines on surface, biocompatible	OVA	N.A.	Sustained anti-OVA IgG, IgG1, IgG2a, and IgA immune responses, > 3 months; Bone marrow secretes IgG and IgG1 antibodies, 3.5 months post-vaccination	Immune response	2018 [127]
Sunflower; Lycopodiastrum	Hollow, high vaccine loading, pH-dependent and controlled release, Sunflower: 31 ± 0.03 μm; Lycopodiastrum: 36 ± 0.08 μm	Nobiletin	Sunflower: 54.8 ± 5 mg g^{-1}, Lycopodiastrum: 67.2 ± 4.7 mg g^{-1}; vacuum 3 h	3% alginate-coated SEC: 2 h, negligible release in SGF, 30 h extended release in SIF	Antioxidant, Anti-inflammatory, antitumor	2018 [149]
Ragweed	Open apertures	BSA	12.23±1.44% for 20% w/w BSA with respect to pollen	Uncoated SEC: 2 h, ≈64%, 6 h, ≈87% in SGF; EUD-coated SEC: 2 h, ≈24%, 6 h, ≈76% in SGF	Gastrointestinal cancer	2018 [150]
Sunflower	Hollow, high drug loading, targeted release	NG (Mixture of nobiletin and glycerol monostearate)	770 ± 40 mg g^{-1}	Uncoated SEC: 2 h, 20% in SGF, 60 h, 90% in SIF; Alginate-coated SEC: 2 h, 2% in SGF, 100 h, 90% in SIF	Antioxidant, Anti-inflammatory, antitumor	2020 [151]
Sunflower	Uniform size (29.74±0.11 μm), spiky surface, drug degradation prevention	β-galactosidase	82.75 ± 2.16%, 3 h vacuum	CMP coated SEC: 24 h, 71.01 ± 1.1% in SGF	Lactose intolerance	2020 [135]

(Continues)

TABLE 1 | (Continued)

Pollen	Characteristics	Drug	Loading	Release	Target problem	Year[Ref.]
Sunflower	Hollow, drug denaturation prevention	β-galactosidase	N.A.	24 h, ≈72%, in SGF	Lactose intolerance	2020 [145]
Lycopodium	Uniform size (≈20 µm in size), controlled release, probiotic proliferation	*L. casei* cells	30.87% for mixed SECs: silica particle-spherical (20 µm), vacuum	6 h, proliferative-released nature	Gut health	2021 [152]
Sunflower; Chamomile	Nanoporous surface, sunflower: tricolporate and echinate structure (26-50 µm); Chamomile: echinate structure (13-25 µm)	N.A.	N.A.	N.A.	N.A.	2021 [153]
Lycopodium	Reticulate surface with trilete tetrad markings, uniform size (≈28 µm), bioavailability	Metformin	29.83 ± 0.83%, vacuum	Uncoated SEC: 2 h, 25% in SGF, 9.5 h cumulative release, ≈84% in SIF; alginate-coated SEC: 2 h, 19% in SGF, 9.5 h cumulative release, 76% in SIF	Type 2 diabetes	2021 [154]
Lycopodium	Uniform size (≈28 µm), honeycomb-like structured surface, pH-dependent release, photoprotection, biocompatible	Vitamin B_9	21.6%, vacuum	1 h, 22.3% in SGF; 1 h, 31% in SIF	Antioxidant, wheezing, asthma, pneumonia	2021 [14]
Date palm	Oblong and oval-elliptic shaped, uniform size, bioavailability, targeted release	5-Fluorouracil	59.81%, vacuum	Uncoated SEC release: 2 h, ≈47% in SGF, 3 h, ≈54% in SIF; EUD-coated SEC release: 2 h, ≈39% in SGF, 3 h, ≈42% in SIF	Colon cancer	2021 [146]
Pine; Ash tree; Linden	Pine: Winged morphology, presence of elongated aperture and 2 air sacs; Ash tree: Reticulated-patterned surface, spheroidal and tricolpate shaped; Linden: Perforated and reticulate-patterned surface, tricolporate shaped	BSA	Pine: 3.92%, Ash tree: 7.77%, Linden: 10.23%; centrifuge	N.A.	N.A.	2022 [131]

(Continues)

TABLE 1 | (Continued)

Pollen	Characteristics	Drug	Loading	Release	Target problem	Year[Ref.]
Lycopodium	Reticular-patterned and trilete scars (Y-shaped) surface, uniform size (20–25 μm), narrow and multi-directional channel (20–40 nm), targeted release, reduced drug-induced ulcers	Diclofenac sodium	50.33 ± 1.60%, vacuum	Biphasic release: 2 h, 52.67%, 24 h, 70.91% in GI tract environment	Gastric ulcer, dental pain, osteoarthritis, ankylosing spondylitis	2022 [142]
Lycopodium	Reticular-patterned and trilete scars (Y-shaped) surface	Aspirin (acetylsalicylic acid)	53.4%, three cycles of probe sonication	10 h, 51.7% in SGF; 10 h, 66.9% in SIF	Anti-inflammatory	2022 [155]
Sunflower	Hollow, uniform size (≈35 μm), spiny surface, self-propulsion, tissue adhesion	Berberine hydrochloride	N.A.	12 h, burst release in GI tract; 60 h, ≈60% in GI tract	Gastric ulcer	2024 [138]
Sunflower	Uniform size, spiny and porous surface, mucoadhesive, biosafe	Pirarubicin	45.3 ± 1.43%	Uncoated SEC release: 5 min, 80%, 30 min, 100% in artificial urine; Alginate-coated SEC release: 150 min, ≈50%, 600 min, ≈80% in artificial urine	Bladder cancer	2024 [122]
Chestnut; Viper's Buglosses; Sheep's Bit; Poppy; Amaranth; Sun Rose; Rock Rose	Chestnut: Ellipse shape, rugulate surface, three tricolporate apertures; Viper's Buglosses: Prolate shape, perforate surface, three tricolporate apertures; Sheep's Bit: Spheroidal shape, perforate surface, three triporate apertures; Poppy: Spheroidal shape, perforate surface, three tricolpate apertures; Amaranth: Spheroidal shape, perforate surface, more than six pantoporate apertures; Sun Rose: Spheroidal shape, perforate surface, three tricolporate apertures: Rock Rose: Spheroidal shape, Reticulate surface, three tricolporate apertures	5-Fluorouracil	18 ± 1 – 28 ± 1%, vacuum	24 h, 69 ± 4% − 88 ± 1% in sequential SGF, SIF, and simulated colon fluid	Cancer Treatment	2025 [156]

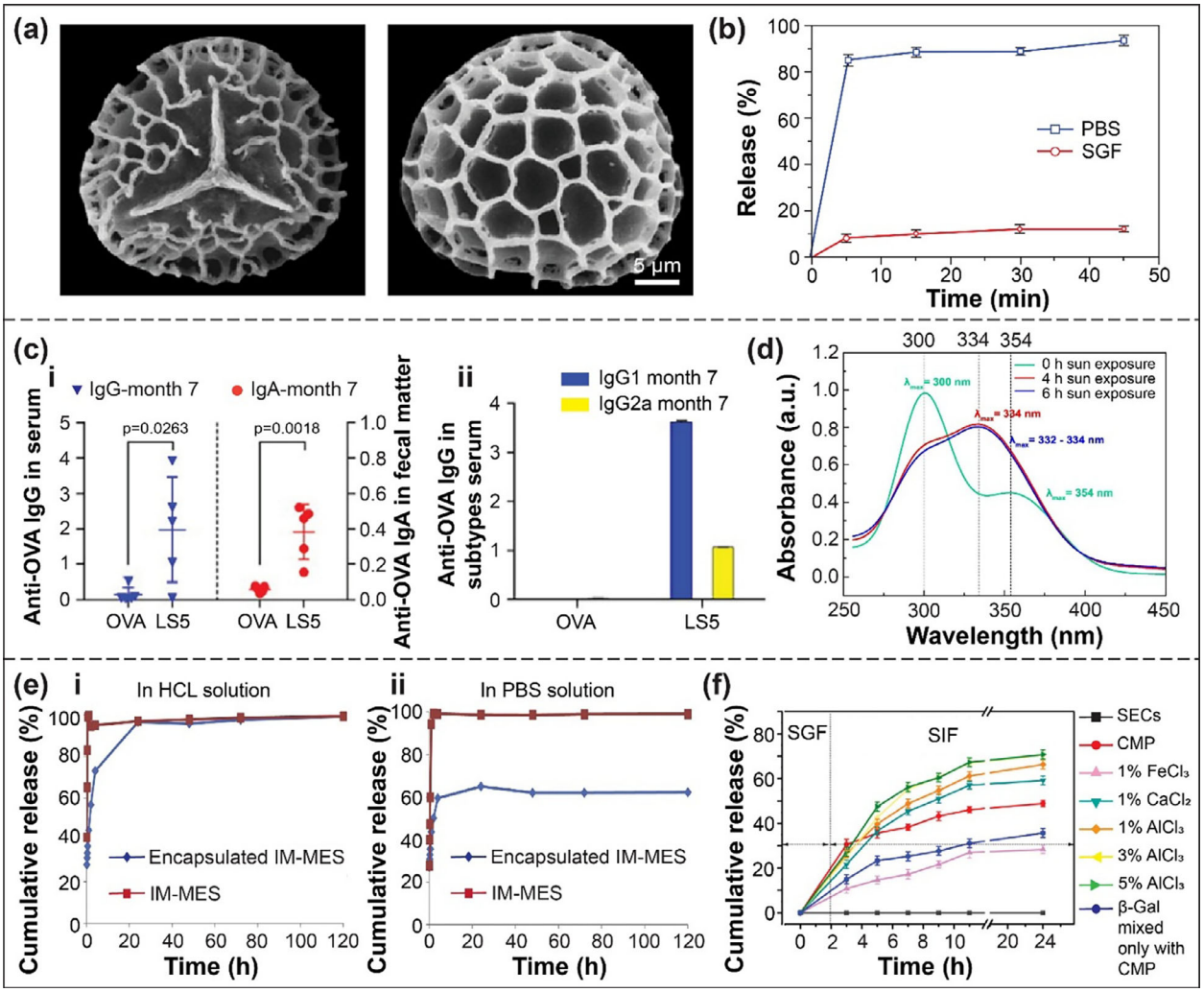

FIGURE 5 | Evaluation of SEC's potential in drug delivery applications. (a) SEM image of lycopodium pollen (i, Y-shaped/trilete scars; ii, reticulated-pattern structure) (reproduced with permission [141], Copyright 2016, Elsevier). (b) Release profile of ibuprofen-loaded lycopodium SEC in simulated gastric fluid (SGF) and simulated intestinal fluids (SIF) environment (reproduced with permission [123], Copyright 2013, Royal Society of Chemistry). (c) Sustained systemic and mucosal immune response for ovalbumin (OVA)-loaded SEC (LS5, 100 μg OVA + 5 mg SEC). OVA is orally vaccinated on a group of mice ($n = 5$) on day 0 and 28 with or without 5 mg lycopodium SEC. Anti-OVA immunoglobulin G (IgG) and immunoglobulin A (IgA) were analyzed 7 months later through serum and decal droppings (i, Anti-OVA IgG in individual mouse serum (dilution 1:400), and anti-OVA IgA in individual mouse fecal droppings (dilution 1:5); ii, Anti-OVA IgG subtypes of pooled serum samples (dilution 1:400) in the seventh month) (reproduced with permission [124], Copyright 2014, Elsevier). (d) UV-Vis spectra on folic acid's photostability under sunlight exposure with pure folic acid at varying exposure times (reproduced with permission [14], Copyright 2021, Elsevier). (e) Release profiles of imatinib mesylate-loaded SEC (Encapsulated IM-MES) against imatinib mesylate (IM-MES) (I, in HCL solution; ii, in PBS solution) (reproduced with permission [133], Copyright 2017, Elsevier). (f) In vitro release profiles of β-galactosidase coated SECs with Carboxymethylpachymaran-zein (CMP) or CMP/metal ion obtained from the incubation for 2 h in SGF and 22 h in SIF environment. (reproduced with permission [145], Copyright 2020, American Chemical Society).

of PLGA as a bioresorbable surgical device gradually ventured out into polymeric biomaterial usage for cosmetics, food, DDS, and agriculture. Unlike their natural counterparts, synthetic polymers offer enhanced control over degradation kinetics, drug release profiles, and structural customization, enabling tailored design for diverse therapeutic contexts. Following the adoption of synthetic microcarriers for drug delivery in the 1990s, PLGA and PLLA were used to create microcarriers due to their favorable biodegradability, allowing safe degradation in vivo and eliminating the need for surgical removal [17, 158]. The first FDA-approved formulation involving PLGA was a long-acting injectable named Lupron Depot delivering leuprolide acetate for 1 month in 1989. Importantly, many of these polymers (e.g., PLGA, PLLA) are already FDA-approved, supporting their translational viability in clinical settings. In the present day, over 20 PLGA-based biodegradable MSs have been approved for use in the market [159]. The earliest and most common fabrication techniques for synthetic polymer microcarriers involved solvent evaporation and emulsion methods to form solid MSs to encapsule drugs [23, 159].

The integration of synthetic polymer chemistry with microfabrication techniques such as microfluidics, emulsion templating, and photolithography has further expanded the functional landscape of these microcarriers. Applications now span sustained drug delivery, gene therapy, vaccine development, and scaffold-based tissue regeneration. GelMA, for instance, bridges the gap

between synthetic control and biological mimicry by combining the photocrosslinkability of synthetic hydrogels with cell-adhesive motifs retained from its gelatin backbone. Meanwhile, PLGA and PLLA MSs continue to serve as long-acting drug depots and biodegradable scaffolds in orthopedic and oncology-related treatments. As the field advances, synthetic polymer-based microcarriers are increasingly employed in multifunctional systems incorporating stimuli-responsiveness, bioactive coatings, or nanoscale co-encapsulation, positioning them as versatile and scalable tools for precision medicine.

5.1 | PLGA

PLGA, an FDA-approved biodegradable polymer (Figure 6a-i) is extensively utilized in the delivery of drugs, proteins, and macromolecules, thanks to its favorable biocompatibility, mechanical strength, and sustained-release properties [160, 161]. Its degradation profile enables non-surgical, long-term drug release, while its physical characteristics, such as polymer molecular weight, lactide-to-glycolide ratio, and drug concentration, can be precisely modulated to control specific release intervals [162, 163]. With technological advancements in the 21st century, PLGA fabrication techniques have evolved into more precise fabrication techniques, including microfluidics and electro-spraying, allowing for better control over particle size and drug release profiles for cancer treatment [159].

PLGA MSs have emerged as a versatile drug delivery platform capable of achieving controlled release profiles while simultaneously improving therapeutic outcomes [164]. In a representative study, ceftiofur encapsulated within PLGA MSs (PLGA-cef) demonstrated superior efficacy compared to the free drug formulation. Specifically, PLGA-cef treatment markedly reduced the total leukocyte count in infected models (from approximately 11 $\times$ 10^3 per μL in untreated infection down to ≈5 $\times$ 10^3 per μL), nearly restoring values to the non-infected baseline (Figure 6b-i). Similarly, a substantial decrease in polymorphonuclear cell infiltration, with PLGA-cef reducing neutrophil counts from over 6 $\times$ 10^3 per μL in the infected control to ≈2.5 $\times$ 10^3 per μL, outperforming free ceftiofur (Figure 6b-ii). These data highlight not only the enhanced anti-inflammatory and antibacterial potency of PLGA-based MSs but also their ability to deliver therapeutics in a sustained and bioavailable manner, underscoring their translational promise for infection management and beyond. Concurrently, PLGA microcarriers featuring collagen patchy domains exhibit uniform size (≈165 μm diameter), maintain structural integrity for up to 3 weeks in aqueous media, and enhance mesenchymal stem cell proliferation by 3.7-fold and osteogenic marker expression by up to 2.0-fold [165]. These properties, stemming from the rough, collagen-rich surface and stable PLGA core, underscore the potential for controlled, prolonged drug release and cell regulation, key advantages for advanced cancer therapy where sustained delivery and tumor-targeted cell interaction are critical.

Caputo et al. [166] employed sorafenib-loaded PLGA nanoparticles (PS) to enhance the therapeutic delivery of sorafenib in hepatocellular carcinoma. The particles were synthesized through an emulsion-solvent evaporation method, yielding uniform nanoparticles with an average size of ≈248 nm and high encapsulation efficiency (≈89.7%) (Figure 6c). The in vitro evaluation demonstrated superior cytotoxic performance of PS, with cell viability reduced to 17% at 7.5 μM after 168 h, markedly outperforming the free drug. Moreover, optical fiber-triggered release experiments showed that under 365 nm UV irradiation, the PLGA carriers enabled localized and on-demand release of sorafenib directly to the hepatic region. Collectively, these findings underscore the potential of PLGA-based MSs as a minimally invasive, light-responsive drug delivery platform with improved therapeutic efficacy in liver cancer treatment. Moreover, porous PLGA scaffolds functionalized with cytomodulin have demonstrated improved hydrophilicity, surface roughness, and pore density, resulting in 80% wound closure within two weeks in a mouse model. This approach significantly reduces inflammation and stimulates fibroblast proliferation, exemplifying PLGA's utility in expediting wound repair [167]. Numerous studies have demonstrated the utility of PLGA as a microcarrier. For example, Chen et al. [165] developed a microfluidic approach exploiting interfacial instability to generate the monodispersed PLGA MSs with controlled drug release dynamics. On the contrary, Sheffey et al. [168] reviewed PLGA particle's clinical adoption in 2020, noting its absence in approved intravenous drug delivery formulations while emphasizing its potential for controlled-release applications. Further demonstrating the versatility of PLGA-based systems, etoricoxib-loaded PLGA microparticles (5–84 μm) exhibited sustained drug release over approximately 30 days (drug loading 2.2–6.9%, encapsulation efficiency 37.8–60.2%), with a triphasic release profile (~5% at 7 d, ≈70% at 16 days, and complete release by 28 d) [169]. In a rheumatoid arthritis mouse model, a single subcutaneous administration showed superior efficacy compared to oral and unencapsulated etoricoxib suspension treatments, reducing joint inflammation, improving synovial histology toward normal structure, and showing no significant organ toxicity.

5.2 | PLLA

PLLA, a biodegradable and biocompatible synthetic polymer with a molecular weight of 40–50 kDa (Figure 6a-ii), is widely recognized for its low toxicity, mechanical stability, and anti-infective properties [170, 171]. Owing to its molecular weight, PLLA evades phagocytosis by macrophages, thereby prolonging circulation time and simplifying injection protocols [172]. Upon administration, PLLA microparticles elicit a subclinical inflammatory response, which is subsequently encapsulated by proliferating macrophages [173]. Over approximately three months, PLLA degrades into lactic acid, which is further metabolized into carbon dioxide and water or synthesized into glucose, thus reinforcing its minimal toxicity profile [174].

Recent advances in PLLA-based MS systems have demonstrated the utility of double-walled architectures (Figure 6d) for controlled drug release [175]. In this study, etanidazole, a highly water-soluble radiosensitizer, was encapsulated within PLGA cores surrounded by a PLLA shell, thereby minimizing the initial burst (<5%) and enabling sustained release for up to three weeks. The release profile revealed a biphasic pattern: an initial diffusion-controlled phase, followed by a degradation-mediated phase that extended the drug release period. Importantly, gamma irradiation at sterilization doses (25 kGy) accelerated polymer

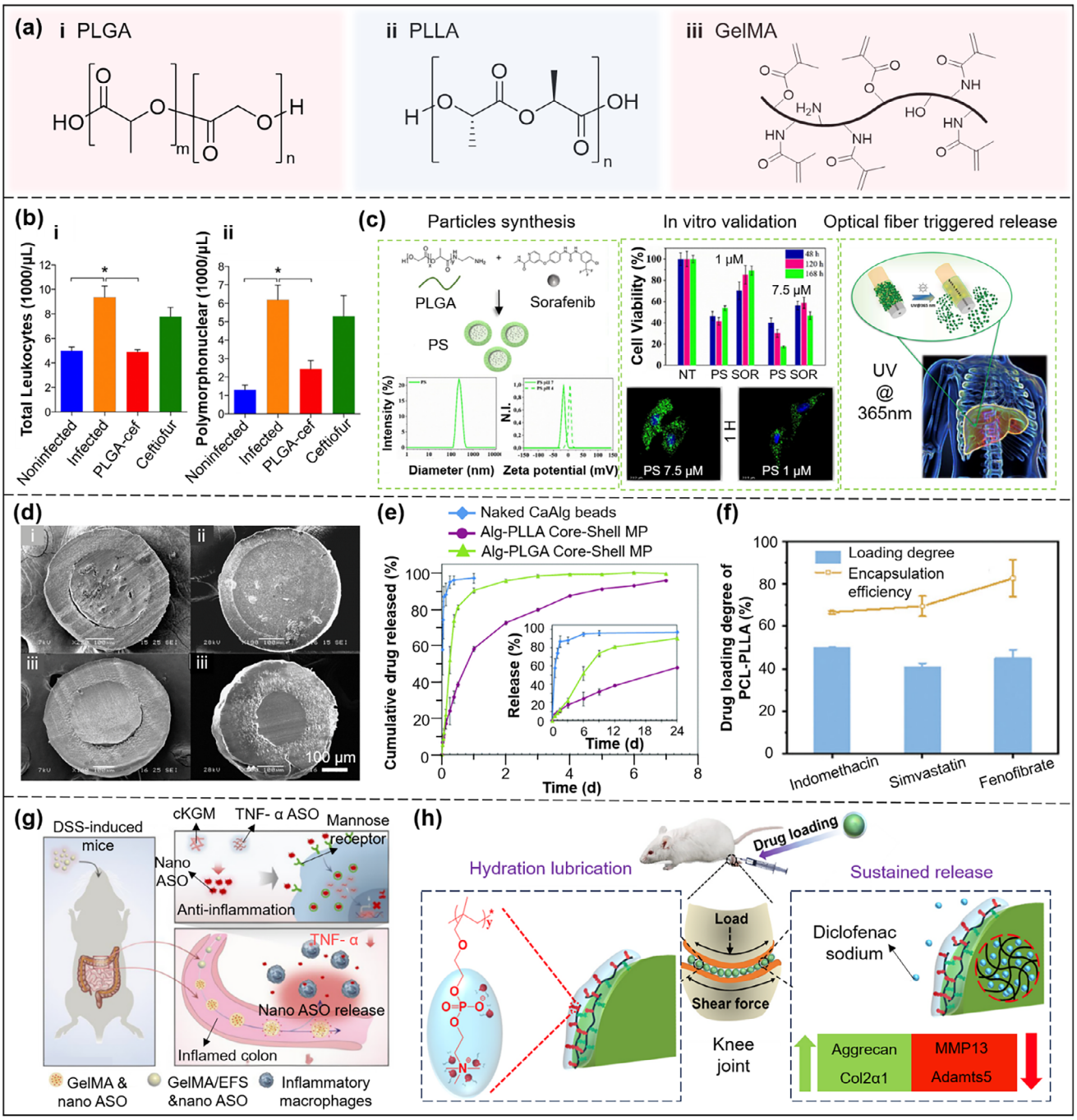

FIGURE 6 | Synthetic polymer-based microcarrier platforms for drug delivery and regenerative applications. (a) Chemical structure of i. Poly(lactic-co-glycolic acid (PLGA), ii. poly-L-lactic acid (PLLA), and iii. gelatin methacryloyl (GelMA). (b) Reduction of leukocyte and polymorphonuclear cell counts by ceftiofur encapsulated within PLGA (PLGA-cef) microspheres (MSs) in infected models (reproduced with permission [164], Copyright 2020, Springer Nature). (c) Schematic representation of PLGA particle synthesis and characterization (left), cytotoxicity and cellular uptake evaluation of sorafenib-loaded PLGA carriers (PS) (middle), and optical fiber-assisted localized release of sorafenib in hepatic tissue (right) (reproduced with permission [166], Copyright 2023, Taylor & Francis). (d) SEM images of cross-sections of double-walled MSs: i. etanidazole-loaded, PLLA–PLGA (2:1), ii. blank, PLLA–PLGA (1:1), iii. blank, PLLA–PLGA (2:1), iv. blank, PLLA–PLGA (2.5:1). (reproduced with permission [175], Copyright 2002, Elsevier). (e) Comparative release profile of metoclopramide hydrochloride from alginate-PLGA/PLLA microparticles (Alg-PLGA/PLLA MPs) and calcium alginate (Ca-Alg) beads (reproduced with permission [176], Copyright 2013, Royal Society of Chemistry). (f) Amorphous polycaprolactone-PLLA (PCL-PLLA) copolymer MSs achieving high drug loading (up to 49.6 wt%) by kinetically manipulating emulsion solidification (reproduced with permission [177], Copyright 2024, John Wiley and Sons). (g) Oral delivery of GelMA-based MSs for targeted transport of antisense oligonucleotides (ASO) against tumor necrosis factor-alpha (TNF-α) in dextran sulfate sodium (DSS)-induced inflammatory bowel disease (IBD) (cKGM: Cationic konjac glucomannan, EFS: Eudragit FS30D; reproduced with permission [183], Copyright 2021, Elsevier). (h) Mechanism of GelMA hydrogel MSs in osteoarthritis treatment through hydration lubrication and sustained drug release (Col2α1: collagen type II alpha 1 chain, MMP13: matrix metalloproteinase-13, Adamts5: adamalysin-like metalloproteinases with thrombospondin motifs-5; reproduced with permission [185], Copyright 2021, Elsevier).

degradation and modulated release kinetics, underscoring the feasibility of tailoring therapeutic schedules for concurrent radiotherapy. This work highlights the significance of PLLA/PLGA double-walled MSs in improving encapsulation efficiency (>55%) and achieving more predictable release behavior for a highly water-soluble drug (etanidazole).

Lim et al. [176] developed alginate–PLLA core–shell MSs, where alginate served as the hydrogel core and PLLA as the hydrophobic shell, to encapsulate metoclopramide hydrochloride as a model drug. This design achieved more than a two-fold increase in encapsulation efficiency (66.5% vs 32.3%) compared with monolithic PLLA MSs. The cumulative release profiles of naked calcium alginate (CaAlg) beads, Alg–PLGA, and Alg–PLLA core–shell MSs (Figure 6e) demonstrated that CaAlg beads released their drug payload completely within one day, whereas Alg–PLGA and Alg–PLLA MSs suppressed the initial burst release and provided sustained release for approximately 4 and 7 d, respectively. While CaAlg beads released the drug completely within 6 h, Alg–PLLA MSs exhibited suppressed burst release within the first 24 h and sustained release for up to 7 d, significantly longer than Alg–PLGA MSs (≈4 d). This prolonged release is attributed to the higher crystallinity and hydrophobicity of PLLA, which restricts water penetration and drug diffusion. Collectively, these findings highlight PLLA-based core–shell MSs as a promising carrier system for stable and long-term delivery of water-soluble therapeutics. Wei et al. [177] systematically engineered PLLA-based MSs to achieve high therapeutic payloads by modulating the kinetics of emulsion droplet solidification, overcoming the long-standing limitation of low drug loading capacity in polymeric carriers. The system achieved notable drug loading degrees across multiple therapeutics—indomethacin, simvastatin, and fenofibrate—with encapsulation efficiencies increasing progressively from ≈70% to nearly 90% (Figure 6f). Specifically, while the absolute drug loading degree remained relatively consistent (≈40–50%), the encapsulation efficiency demonstrated marked improvement for fenofibrate, underscoring the ability of this strategy to enhance drug retention within the PLLA matrix. These results highlight the promise of PLLA MSs as high-capacity drug delivery vehicles capable of accommodating hydrophobic therapeutics with improved stability and clinical applicability.

In parallel, PLLA-based microcarriers incorporating galantamine (GAL) adsorbed onto hierarchical porous carbon (HPC) demonstrate up to 30% drug loading and form ≈1300 nm particles, extending GAL release beyond 9 d relative to the unencapsulated drug [178]. By stabilizing GAL in an amorphous state and supporting intranasal administration, these HPC-loaded microcarriers (verified to release 21.5% GAL from HPC) efficiently target the hippocampus, thereby offering a promising therapeutic platform for Alzheimer's disease. Consistent with these sustained delivery characteristics, PLLA MSs loaded with naringin achieved an encapsulation efficiency of approximately 70% and exhibited sustained drug release of about 50% over 35 days, compared to free naringin releasing over 80% within 16 h [179]. The gradual degradation of PLLA decreased the local pH from 7.4 to around 6.6, enhancing the solubility and bioactivity of naringin while maintaining cell viability above 95% and promoting osteogenic differentiation and mineralization of bone marrow mesenchymal stem cells. These findings highlight the potential of PLLA-based MSs for bone repair applications through prolonged and controlled stimulation of bone formation in vitro.

5.3 | GelMA

GelMA, a gelatin-based biomaterial, has been extensively studied as a promising alternative to Matrigel for 3D cell culture and a wide range of bio applications [180]. It is synthesized by reacting gelatin with methacrylic anhydride (MAA) (Figure 6a-iii), allowing researchers to fine-tune the degree of methacryloylation by adjusting the MAA-to-gelatin feed ratio. This customization substantially influences the biophysical and chemical properties of GelMA. Under UV or visible light, GelMA cross-links with water-soluble photoinitiators to form stable hydrogels that maintain structural integrity at physiological temperatures, rendering it particularly appealing for various drug delivery applications [181, 182].

Gan et al. [183] developed GelMA-based MSs as an oral drug delivery platform for IBD, enabling efficient encapsulation and controlled release of antisense oligonucleotides (ASOs) targeting tumor necrosis factor-alpha (TNF-α) (Figure 6g). Orally administered GelMA/ASO and GelMA/EUD FS30D/ASO MSs first transit through the GI tract and accumulate specifically in the inflamed colon of DSS-induced colitis mice. Within the colon, the GelMA MSs gradually degrade to release nanoscale antisense oligonucleotide complexes, which are efficiently internalized by inflammatory macrophages through mannose receptor-mediated endocytosis. This process leads to a pronounced reduction of tumor necrosis factor-alpha secretion at the local inflammatory site, thereby suppressing the inflammatory cascade and promoting mucosal tissue repair. These results collectively demonstrate the high targeting specificity and therapeutic efficacy of GelMA MSs as nucleic acid carriers for GI diseases. Also, recent advancements in double-emulsion microfluidic fabrication have enabled the development of GelMA-PLGA core–shell microparticles capable of simultaneously encapsulating hydrophilic DOX (500 μg mL^{-1}) and hydrophobic camptothecin (500 μg mL^{-1}) within a solid hydrogel core and a tunable polymer shell (thickness ≈22–60 μm) [184]. This approach ensures high drug encapsulation efficiency while minimizing burst release. By precisely modulating the shell-to-core ratio, these microparticles exhibit enhanced synergistic cytotoxic effects, reducing cell lines and human colon carcinoma (HCT116) cell viability to below 20% and human hepatoma (HepG2) cell viability to below 10%. Furthermore, their controlled polymer degradation facilitates sustained drug release, thereby significantly improving therapeutic efficacy. Han et al. [185] engineered injectable GelMA-based hydrogel MSs as a dual-functional platform for osteoarthritis therapy, simultaneously enhancing joint lubrication and providing sustained drug delivery (Figure 6h). These MSs reduce friction at the cartilage surface through hydration lubrication while resisting mechanical shear forces within the knee joint. In parallel, diclofenac sodium loaded within the GelMA matrix is gradually released in a controlled manner, which suppresses pro-inflammatory and catabolic mediators such as matrix metalloproteinase-13 (MMP13) and adamalysin-like metalloproteinases with thrombospondin motifs-5 (Adamts5) while upregulating cartilage-protective markers including aggrecan and collagen type II alpha 1 chain (Col2α1). This combination of

mechanical protection and localized therapeutic delivery underscores the potential of GelMA MSs as a biomimetic treatment strategy for osteoarthritis.

5.4 | Other Polymeric Materials

Other polymeric materials for microcarriers, including poly(N-isopropylacrylamide) (pNIPAAm), PEG, PEG-conjugated polymers, polyethyleneimine (PEI) polyplexes, trimethylolpropane ethoxylate triacrylate (TMPTA), and polycaprolactone (PCL), provide highly versatile platforms for targeted and controlled drug delivery applications [186–189]. The efficiency of these systems depends not only on environmental factors such as pH and temperature but also on specific properties of the microcarriers, including size, shape, and polymer molecular weight [188]. Among these materials, pNIPAAm microgels are particularly noteworthy for their temperature-responsive behavior. These microgels can encapsulate non-polar molecules in oil droplets and polar molecules within the hydrogel network. Upon heating, the microgels contract, releasing both types of cargo and showcasing their potential for stimuli-responsive and multi-drug delivery applications [190]. In addition, TMPTA microparticles with a reductively labile cross-linker have demonstrated their ability to release DOX in reducing environments. This targeted approach has been shown to effectively kill HeLa cells in vitro, highlighting its promising application in cancer treatment [191].

6 | Conclusion and Outlook

In conclusion, microcarriers hold significant promise in the field of drug delivery. The integration of polysaccharides, proteins, SECs, and synthetic polymers offers a versatile platform for the controlled and targeted release of therapeutic agents. Polysaccharides, known for their abundance, biocompatibility, and biodegradability, offer a controlled and sustained release mechanism for encapsulated drugs. The incorporation of alginate and chitosan with specific binding affinities or functional groups can further improve targeting and facilitate the controlled release of therapeutic agents. Protein-based microcarriers, including collagen, gelatin, and SF, have gained critical attention for drug delivery due to their ability to mimic the natural extracellular environment and facilitate cell–matrix interactions. Collagen and gelatin, derived from natural sources, provide structural integrity and can be easily functionalized to enhance precision drug delivery. SF offers unique advantages, such as high mechanical strength, slow degradation rates, and the ability to incorporate both hydrophilic and hydrophobic drugs. SEC, as a natural microcarrier derived from pollen grain, possesses exciting potential for advancing therapeutic intervention due to its robust structure and versatility in incorporating a wide variety of therapeutic agents. The porous structure of sporopollenin allows for controlled release, extending to the delivery of both hydrophilic and hydrophobic drugs, including proteins, peptides, and nucleic acids. Furthermore, SEC microcarriers exhibit low toxicity and can be engineered to bypass biological barriers, providing opportunities for precision medical therapy. Synthetic polymer-based microcarriers such as PLGA and PLLA also offer a promising avenue for advanced drug delivery with versatile biodegradable capabilities for controlled drug release, tissue regenerative applications, and stimuli-responsive therapies.

The use of these materials represents a hallmark of technological advancement and future potential of microcarriers, characterized by high modularity and customization to address diverse therapeutic needs, ranging from cancer therapy to vaccine delivery and tissue regeneration. By strategically adopting a highly selective approach to these microcarriers, it is possible to systematically mitigate multifaceted clinical challenges. Highly biocompatible matrices such as chitosan, agarose, collagen, SF, and synthetic polymers like PLGA or PLLA can be utilized to attenuate immunogenicity and bypass adverse inflammatory cascades. Beyond biological tolerance, the use of structurally resilient materials such as SEC, PLGA, and agarose allows for the engineering of robust mechanical properties that suppress premature burst release and maintain stable pharmacokinetics for sustained release. Moreover, leveraging naturally abundant precursors such as alginate and pollen-derived SECs offers a viable pathway to mitigate financial risks and ensure the economic scalability of manufacturing. By reducing prohibitive manufacturing costs, these materials can incentivize the development of novel therapies and significantly broaden patient access to essential treatments for more diseases. The optimization of material properties may impose challenges for controlling molecular interactions, particularly in balancing drug loading, release kinetics, and structural stability within microcarrier systems Nevertheless, smart microcarriers have demonstrated promising research outcomes, and the incorporation of artificial intelligence (AI), particularly machine learning, is expected to further advance therapeutic delivery by enabling data-driven prediction of material properties and rapid screening of large numbers of candidate microcarrier formulations. Specifically, AI can be applied to predict structure-property-performance relationships, such as correlating microcarrier size, porosity, and surface chemistry with drug loading and release kinetics. In addition, inverse design approaches can be employed to optimize formulation parameters to achieve target delivery profiles, while high-throughput virtual screening of candidate delivery systems can significantly reduce experimental effort. By leveraging large experimental and computational datasets, AI can accelerate the identification of optimal microcarrier designs, thereby reducing reliance on empirical trial-and-error strategies and enabling a more efficient and predictive development process [192–194].

Collectively, current evidence suggests that several microcarrier systems exhibit favorable biosafety characteristics and emerging preclinical efficacy, highlighting their potential for clinical translation. Recent advances have explored the development of composite microcarriers to integrate complementary properties within a single platform. Alginate-based microbeads combined with gelatin have shown promising biosafety and injectability through a 21-gauge needle with low breakage, and a post-thaw viability of mesenchymal stromal cells of >80% over a week in culture after cryopreservation [195]. A 2024 study evaluating agarose-collagen composite MS implants for skin tissue regeneration demonstrated blood compatibility, enhanced in vitro cellular proliferation, adhesion, and migration, and in vivo wrinkle reduction, improved skin metrics in photoaged mice by stimulating fibroblast encapsulation and collagen regeneration, exhibiting a favorable biosafety profile for dermal implantation application [196]. Moreover, these microcarriers can also be involved in combination therapy development, with the capacity to co-deliver multiple drugs or therapeutic agents, therefore offering

promising opportunities to achieve synergistic therapeutic effects and advance precision medicine.

Acknowledgements

This work was supported by the Ministry of Education (MOE) in Singapore under the MOE AcRF Tier 3 grant (Grant No. MOE-MOET32022-0002) as well as the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant No. HI22C1394) and Ministry of Agriculture, Food and Rural Affairs (Grant No. RS-2024-00403067). We thank our colleagues in the Translational Materials Innovation Group (TMIG) for their long-term contributions to the development of the pollen research field.

Funding

This work was supported by the Grant Nos. MOE-MOET32022-0002, HI22C1394, and RS-2024-00403067.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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