Chen *et al.*
Journal of Leather Science and Engineering (2022) 4:3
https://doi.org/10.1186/s42825-021-00075-y

Journal of Leather Science and Engineering

REVIEW

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Collagen-based materials in reproductive medicine and engineered reproductive tissues

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Abstract

Collagen, the main component of mammal skin, has been traditionally used in leather manufacturing for thousands of years due to its diverse physicochemical properties. Collagen is the most abundant protein in mammals and the main component of the extracellular matrix (ECM). The properties of collagen also make it an ideal building block for the engineering of materials for a range of biomedical applications. Reproductive medicine, especially human fertility preservation strategies and reproductive organ regeneration, has attracted significant attention in recent years as it is key in resolving the growing social concern over aging populations worldwide. Collagen-based biomaterials such as collagen hydrogels, decellularized ECM (dECM), and bioengineering techniques including collagen-based 3D bioprinting have facilitated the engineering of reproductive tissues. This review summarizes the recent progress in applying collagen-based biomaterials in reproductive. Furthermore, we discuss the prospects of collagen-based materials for engineering artificial reproductive tissues, hormone replacement therapy, and reproductive organ reconstruction, aiming to inspire new thoughts and advancements in engineered reproductive tissues research.

Keywords: Collagen-based biomaterials, Leather and collagen, Leather tanning process, Reproductive medicine, Reproductive tissues

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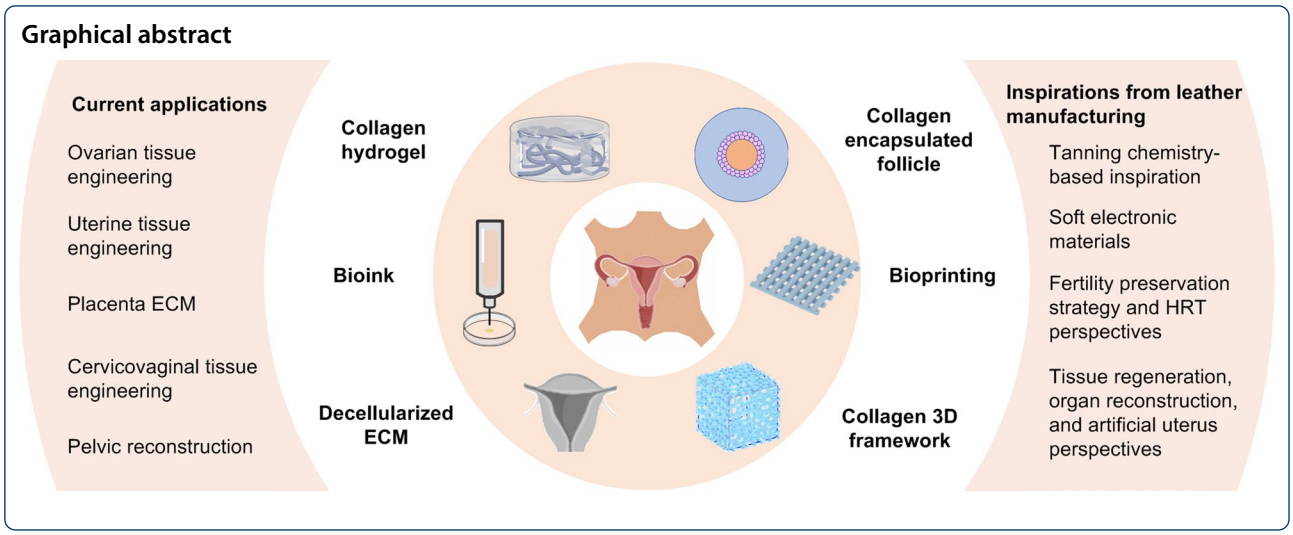

1 Introduction

Collagen is an important renewable resource that has been used for thousands of years in leather manufacturing. To turn animal hide into wearable leather, a complex and scientific preparation process is required, where plant tannins or metal ions are used to crosslink the active groups in collagen fibers. This process creates a more porous internal microstructure, reduces the bonds between collagen fibers, reduces leather expansion in water, improves the moisture and heat resistance, and also improves the chemical corrosion resistance [1]. Additionally, the processes and materials used in leather making can provide fundamental inspiration and guidelines for further developing biomaterials based on collagen or collagen derivatives (e.g., gelatin) [2]. So far, more than 29 types of collagen molecules have been identified and studied, which together provide a powerful toolbox for the preparation of multifunctional biomaterials [3]. Due to the high biocompatibility and versatile chemical properties, collagen has been widely used in the preparation of biomaterials and the treatment of various diseases [4].

One of the most concerning issues for societies around the world is population aging. Recent environmental and social structural changes have led to the rapid decline of human fertility and accelerated the global demographics shift towards an aging population. Population aging tends to lower both labor-force participation and savings rates, which together raise concerns about slowing economic growth in the future. Though behavioral responses (for example, greater female labor-force participation) and policy reforms (for example, an increase in the legal age of retirement) can mitigate the economic consequences of an older population, the key to resolving the growing issue of population aging in a sustainable future is to increase fertility rates and birthrates. Currently, around 8-12% of reproductive-aged couples suffer from infertility worldwide, of which women contribute to approximately half of the cases [5]. Over the past few decades, reproductive medicine has developed rapidly, with the introduction of in vitro fertilization (IVF) in 1978 [6], the cryopreservation of human oocytes in 1986 [7], intracytoplasmic sperm injection (ICSI) in 1992 [8], and the in vitro maturation (IVM) of oocytes in 1994 [9]. Meanwhile, there has also been remarkable progress in the transplantation of reproductive organs, including ovary [10], uterus [11], and vagina [12] transplantation. Novel materials engineering approaches are needed to facilitate continued progress in this space and collagen-based biomaterials have been applied in the recovery and regeneration of injured or damaged reproductive tissue [13] and contraception [14, 15].

In this review, we aim to comprehensively summarize and discuss the current progress and future possibilities of collagen-based materials for reproductive medicine (Fig. 1). Besides, gelatin, a derivative of collagen generated through hydrolyzing the natural triple-helix structure into single-strand polypeptides, is included in this review due to its collagen-like properties and high potential in tissue engineering. This review highlights the interfaces between regenerative biomaterials and traditional leather science. Since collagen and tanning chemistry have been used throughout human history for thousands of years, the experience and techniques from leather science can provide fundamental guidelines and inspiration for the design and engineering of the next generation of reproductive biomaterials.

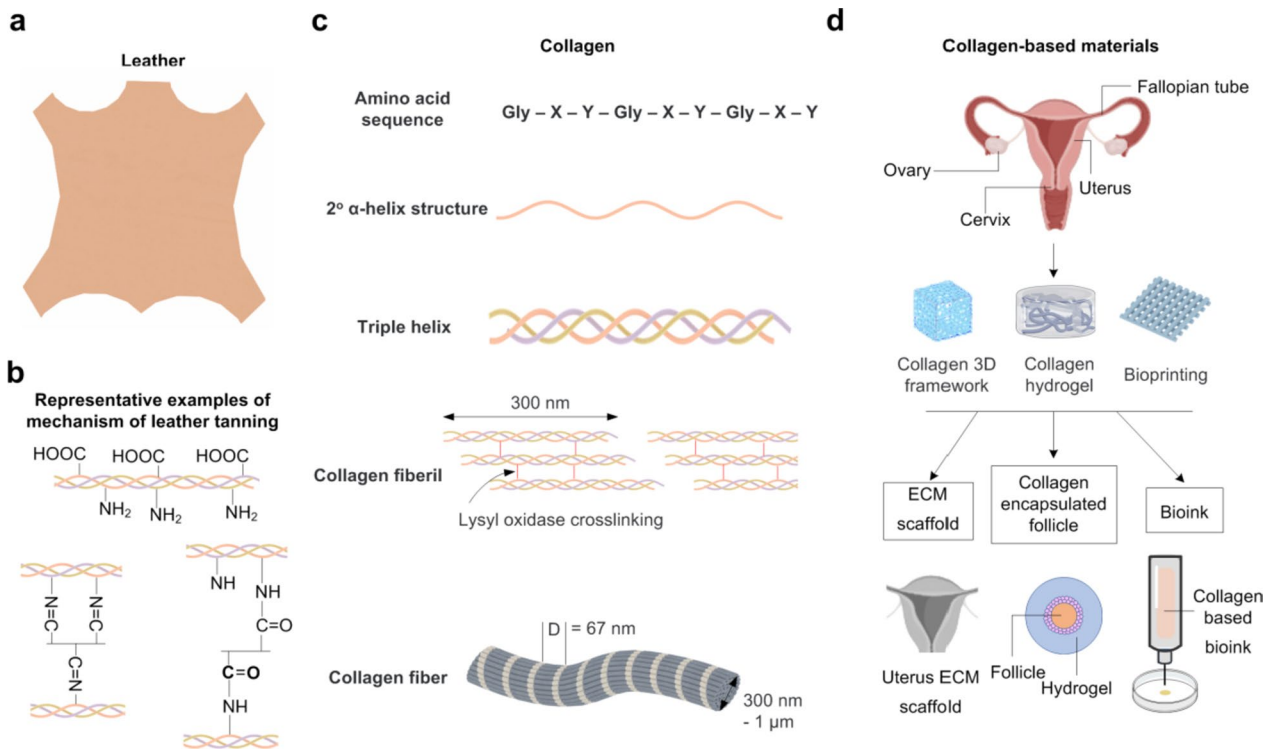

Fig. 1 **a**, **b** Illustration of leather and representative examples of leather tanning mechanisms. **c** Schematic drawing of the hierarchical structures of collagen [19]. Reproduced with permission from [19]. **d** Collagen-based materials and their use in reproductive medicine

2 Collagen-based materials in reproductive medicine

Collagen protein has a highly complex and hierarchical conformation, which is organized as a quaternary structure, where a triple helix super secondary structure is the most defining feature of collagen (Fig. 1c). The primary structure of collagen is characterized by the fixed presence of glycine (Gly), which is found in every amino acid triplet. Proline (Pro) and hydroxyproline (Hyp) are also frequently found, as Gly-Pro-Hyp is the most common sequence in collagen (approximately 12%). Additionally, Gly-X-Hyp and Gly-Pro-Y sequences together account for another 44% of sequences with the remaining 44% being Gly-X–Y sequences [16]. The α-chains are formed by repetitions of the tripeptide, with a triple-helical domain in the middle, and two non-helical domains at either end of the helix. Three parallel α polypeptide chains coil around each other to form the triple helix structure, which is approximately 300 nm in length and 1.5 nm in diameter and is the fundamental structure of collagen [17, 18]. Collagen fibrils are formed by the self-assembly of collagen molecules through a quarter-stagger package pattern of five triple-helical collagen molecules, where the overlap and gap regions between these collagen molecules result in the ~ 67 nm D-periodicity of collagen fibers [17]. Here, we outline some major models and applications of collagen-based materials in reproductive medicine. We aim to provide a clear understanding of the benefits of collagen-based materials so that there can be further improvement in reproductive tissue engineering.

2.1 Collagen hydrogel scaffolds

Hydrogels are three-dimensional (3D) polymer network structures with high water content, in which the polymer chain maintains structural integrity through physical and chemical crosslinking. Hydrogels are widely used in biotechnology and medicine to deliver cells, drugs, or biologically active molecules, and are also regularly used in cell culture. Cells can be cultured atop a two-dimensional (2D) hydrogel or embedded in a hydrogel as a more complex 3D culture system [20]. Collagen hydrogel is one of the most used naturally derived hydrogels owing to its physical, mechanical, and biological properties. Collagen hydrogels have high water content (over 99%) and demonstrate the ability to gel, swell, self-aggregate, and can be enzymatically degraded [21]. Moreover, they can provide a relatively realistic microenvironment mimic ECM, which allows cell adhesion, proliferation, differentiation, and protein sequestration. However, collagen hydrogels

are not always ideal as scaffold materials because of their weak mechanical strength due to rapid degradation rate in biological environments, opacity, and high shrinkage [22]. It is therefore often necessary to improve the overall performance of collagen hydrogels for tissue engineering.

Crosslinking collagen with other materials (e.g., chitosan [23], polyvinyl alcohol [24], alginate [25], hyaluronic acid [26], polyethylene glycol [27], and fibrin [28]) can significantly enhance the mechanical and biological stability of collagen hydrogels. In addition, gelatin is a derivative of collagen generated through heat or chemical treatment [29] via hydrolyzing the natural triple-helix structure into a single-strand polypeptide. Gelatin retains the cell-binding regions and the biological properties of collagen and is highly water-soluble, biocompatible, biodegradable, and has low immunogenicity [30, 31] making it promising in tissue engineering. To date, there have been many attempts to utilize collagen hydrogels in reproductive medicine and tissue engineering. For example, one study encapsulated the telomerase immortalized human endometrial stromal cells in a collagen I hydrogel and treated it with in vitro hormone exposures. The results suggested that the engineered endometrial stroma could mimic the natural morphological and biochemical changes occurring during secretory and menstrual phases of the menstrual cycle [32]. Another study cultured ovarian follicles in collagen I hydrogel and found that the density and elasticity of the hydrogel could influence follicle survival, growth, development, and hormone production, along with oocyte maturation and ovulation [33]. One study applied a gelatin hydrogel, specifically a pue-loaded gelatin methacrylate (Pue@GelMA) hydrogel, in pelvic organ prolapse (POP) models. This material could alleviate inflammation by reducing the level of inflammatory factors and accelerating the reconstruction and regeneration of the pelvic floor fascia [34]. Still, other studies have reported that transplantation of stem cells with collagen scaffolds [35] or the transplantation of encapsulated autograft ovarian tissue fragments in fibrin-collagen hydrogels [36] helps ovarian survival and recovery. Therefore, collagen hydrogels can be utilized in many fields, including in vitro 3D tissue culture, and the reconstruction and transplantation of reproductive tissues and organs.

2.2 Decellularized ECM

ECM generally refers to the non-cellular substances surrounding the cells in tissues or organs, and mainly consists of structural substances (e.g., collagen, elastin, polysaccharides, and proteoglycans) and functional molecules (e.g., growth factors, cytokines, chemokines). ECM plays an essential role in cell proliferation, differentiation, maturation, cell communication, homeostasis, immunity, and many other biological processes [37]. dECM can be obtained by removing the cellular components of tissues or organs while retaining the 3D structural and biochemical components of the ECM [38]. Different methods can be used to process dECM, including mechanical, chemical, and enzymatic treatment [38]. Moreover, dECM can be modified by physical and chemical crosslinking using chemical crosslinking agents (e.g., carbodiimide (CDI), epoxy compounds, glutaraldehyde, and hexamethylene diamine carbamate (HMDC)) and natural (e.g., genipin (GP), tannic acid, proanthocyanins (PC), and nordihydroguaiaretic acid (NDGA)) crosslinking agents [39–41] to generate various materials (e.g., powders, patches, and hydrogels) [38]. Some consider dECM to be the best choice for tissue engineering among different hydrogels because it has the natural structure and composition of individual tissue and can thus facilitate reseeding cells and cellular reorganization [42].

dECM has been widely applied to engineer reproductive tissue and retain its structure and function. For example, culturing ovarian cells onto the dECM scaffold allows cells to reconstruct follicle-like structures, produce hormones, and even initiate puberty after transplantation, thus preserving and reestablishing female fertility [43–53]. For uterus engineering, decellularized endometrial tissue has been repopulated with endometrial cells successfully, where the viability, proliferation, and hormonal response of endometrial cells have been restored [44, 54–67]. The decellularization of the placentas also has extensive applications in regenerative and reproductive medicine [68–70]. Overall, dECM has been widely applied as a scaffold of choice in reproductive tissue engineering, yet it is challenging to restore the mechanical strength of dECM and postpone the rapid degradation in vivo while maintaining the structural and biochemical function.

2.3 Collagen-based bioinks for 3D printing and bioprinting

Over the past 20 years, 3D printing has been widely applied in biomedicine for medical devices and instruments, and in tissue regeneration, cell culture, and drug discovery and development [71]. 3D printed scaffolds for tissue engineering are porous, polymeric, cell-free scaffolds used for subsequent cell seeding, which are of high accuracy and complexity, and can be produced rapidly [72, 73]. While 3D printing is a cell-free technology, 3D bioprinting is characterized by using cell-laden 'bioinks' to directly build engineered tissues and organs [74]. 3D bioprinting has various advantages, including geometrical freedom, automation, standardization reproducibility, repeatability, realistic microenvironments, and customizability [75]. Therefore, compared with conventional

tissue engineering methods, 3D bioprinting can accurately deposit cells and biomaterials together into precisely controlled architectures.

Bioinks are vital for 3D bioprinting because they should contain the necessary conditions to provide both structural and biochemical support for cell viability and growth. Therefore, bioinks need to have high biocompatibility, printability, and low antigenicity. The most common components of bioinks include ECM proteins (e.g., collagen, gelatin), functional molecules (e.g., growth factors, cytokines), and cells [76]. Currently, collagen, gelatin, and ECM hydrogels are extensively used as components of bioinks in 3D bioprinting of different tissues because of their high biocompatibility, printability, and workability. Nevertheless, these biomaterials need to be modified (e.g., crosslinking) and mixed in suitable proportions to improve the mechanical strength and biological properties before being used as bioinks [2].

Recently, there are emerging studies about the application of 3D bioprinting in reproductive medicine. For example, one study used a gelatin bioink scaffold and isolated small follicles to create a bioprosthetic ovary. They found it could survive, be vascularized, and even preserve ovarian function (i.e., ovulation) and fertility after transplantation [77]. Another study used a gelatin/sodium alginate hydrogel as a bioink for 3D bioprinting a human induced pluripotent stem cell (iPSC)-derived mesenchymal stem cell (MSC)-loaded scaffold to regenerate endometrium. This material could improve the recovery of the endometrial histomorphology and aid the regeneration of stromal, epithelial, and endothelial cells. Moreover, this not only enhanced endometrial receptivity but also restored the ability of implantation and pregnancy maintenance of the injured endometrium [78]. Another study successfully applied an acellular vagina matrix (AVM) hydrogel and seaweed gelatin/alginate hydrogel as bioinks in 3D bioprinting biomimetic vaginal tissue, which showed good biocompatibility, vascularization, epithelization, and differentiation [79]. Similarly, 3D bioprinting of collagen-based material bioinks could be utilized for engineering placenta models [80]. Still, there is a long road ahead for 3D bioprinting reproductive tissues and organs, and bioinks based on collagen-based materials have yet to be fully explored.

3 Current applications of collagen-based biomaterials

Current applications of collagen-based biomaterials in reproductive medicine and engineered reproductive tissues are extensively summarized in Table 1. In general, collagen-based biomaterials demonstrate various advantages in the field of reproductive medicine as they can suspend and support isolated reproductive function cells, have high biocompatibility, and are biodegradable in vivo and in vitro.

3.1 Ovarian tissue engineering using collagen-based biomaterials

With the development of modern medical technology, the survival period of young cancer patients has been significantly extended, however, chemotherapy and radiation therapy are generally gonadotoxic. Therefore, fertility preservation treatment is necessary for young cancer patients who have not yet had children. Re-transplantation after cryopreservation of ovarian tissue is the only option to preserve fertility in prepubertal female patients who required immediate cancer therapy. In addition, for some fertile female patients, re-transplantation of ovarian tissue can preserve the endocrine function of the ovary to reduce the risk of osteoporosis, cardiovascular disease, and vasomotor symptoms. Meanwhile, patients who suffer from decreased ovarian reserve due to the surgical

Table 1 Overview of recent studies in collagen-based materials in reproductive medicine and engineered reproductive tissues

Collagen-based material	Tissue	Application	References
Hydrogel	Ovary	Follicle encapsulation and culture	[33, 81–94]
	Uterus	Endometrial cell culture	[95, 96]
	Fallopian tube	3D organoid culture	[97]
dECM	Ovary	Follicle culture and transplantation	[46, 47, 49, 50, 98–100]
	Uterus	Endometrial, myometrial cell culture, and transplantation	[55–58, 62, 66]
	Placenta	Generate scaffolds	[70, 101, 102]
	Cervicovaginal	Cervicovaginoplasty	[12, 13, 103–106]
Collagen-based bioink	Ovary	Follicle culture and transplantation	[77]
	Placenta	Bioengineered placenta model	[80, 107]
	Pelvic floor	Mesh encapsulation and pelvic floor reconstruction	[108]
Collagen coating Mesh	Pelvic floor	Mesh encapsulation and pelvic floor reconstruction	[108–111]

treatments of benign ovarian tumors and endometriosis could also benefit from fertility preservation treatment.

However, ovarian tissue transplantation faces several problems in clinical practice. The most prominent problem is the risk of disease metastasis and recurrence caused by the potential reintroduction of cancer cells and an initial ischemic injury of ovarian tissue after transplantation [112, 113]. Engineered reproductive tissues provided promising solutions. In the process of ovarian transplantation, any malignant cells should be separated so that only core functional cells are transplanted.

The essential functional component of the ovary is the ovarian follicle in the cortex, and collagen-based materials have been applied to encapsulate ovarian follicles and provide the extracellular support structure for cell growth. The encapsulated oocytes and related somatic cells could successfully survive and secrete hormones in vitro and the mouse transplantation model. The collagen-based bio-materials currently applied for encapsulating follicles are hydrogels primarily comprised of Matrigel (a natural hydrogel secreted by mouse sarcoma cells), alginate (a natural hydrogel derived from algae), and poly(ethylene glycol) (Fig. 2). It has been reported that macroporous alginate scaffolds layered with affinity-bound bone morphogenetic protein-4 could successfully mimic the ovary microenvironment. Porcine primordial follicles could be cultured in these scaffolds to the preantral stage and retain their hormone-secreting function in an immunodeficiency mice xenotransplantation model [93]. Furthermore, isolated ovarian follicles have been seeded in alginate-matrigel matrix scaffolds and transplanted into mice models. After transplantation, the matrix scaffolds were observed to degrade and allowed vascularization around the follicles [91].

During encapsulation and transplantation, hydrogels can exhibit beneficial support for cells. For example, a microfluidic microencapsulation hydrogel encapsulation model was reported to successfully mimic the mechanical characteristics of the mammalian ovary in vitro. A softer 0.5% collagen hydrogel core mimicked the medulla of the ovary, while a harder, and slowly degradable 2% alginate hydrogel shell mimicked the rigid cortex of the ovary. This 3D culture model could effectively transport oxygen and nutrients to the capsulated ovarian follicles (Fig. 2). Finally, the controlled degradation of the capsule could be achieved by alginate lyase encapsulated in PLGA microspheres [114].

Other strategies are also promising, including the use of dECM to assist human ovarian tissue auto-re-transplantation. For example, the dECM materials called AlloDerm (LifeCell Corp.) have been applied in human ovarian tissue re-transplantation following cryopreservation. After the re-transplantation, the patient gained IVF live-birth with subsequent hormone secretion until 2-year after transplantation. AlloDerm is a decellularized product derived from cadaveric or xenographic skin that can be used in tissue reconstruction and plastic surgery [115]. It is possible to construct a decellularized human ovarian scaffolds model from ovarian tissue donated by patients with malignant tumors, and by removing all of the cells from the ECM (including malignant cells), the collagen content of the ovary could be preserved (Fig. 3).

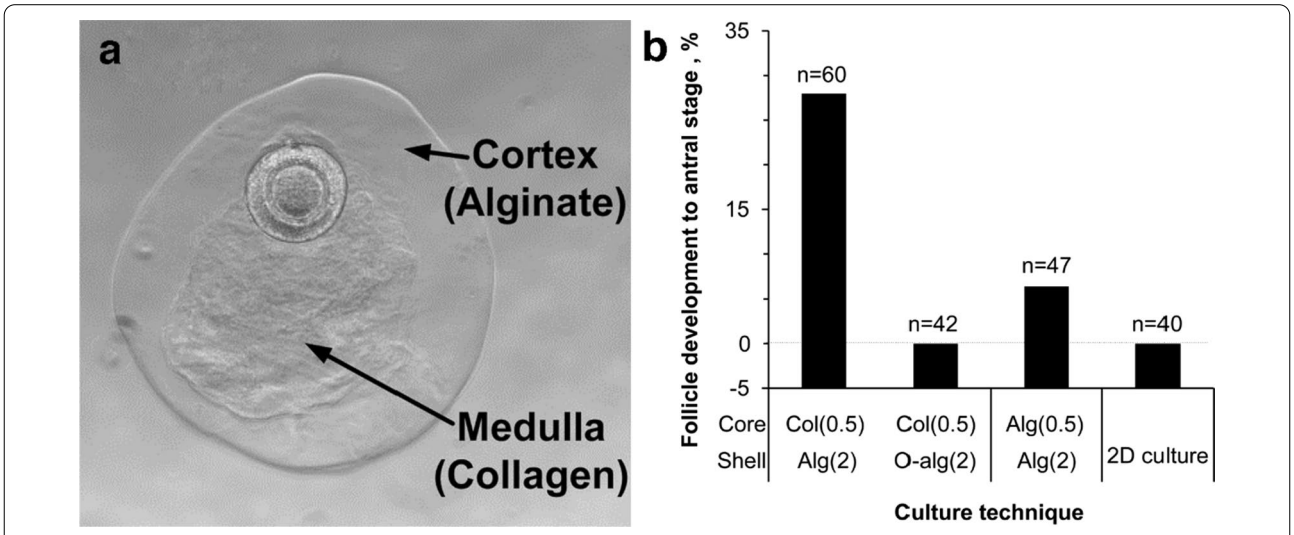

Fig. 2 Collagen-encapsulated follicle. **a** Micrographs of an early secondary preantral follicle encapsulated in a collagen core with an alginate shell. **b** Quantitative data shows the effect of the core (0.5% collagen) and shell (2% non-oxidized alginate) materials is the highest. Collagen (Col), alginate (Alg), oxidized-alginate (O-alg). Reproduced with permission from [114]

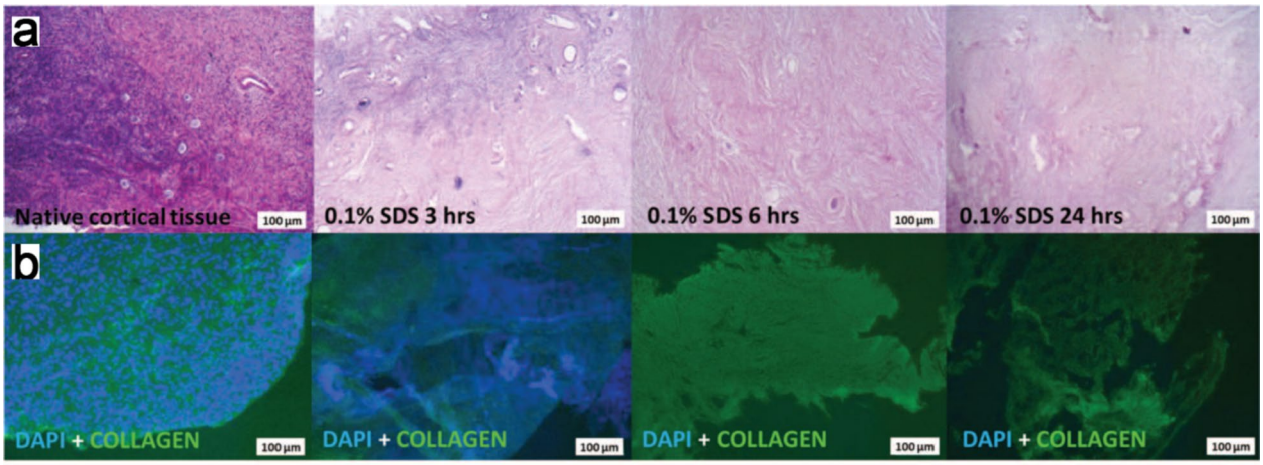

Fig. 3 dECM of human cortical ovarian tissue. **a** PAS staining of human cortical ovarian tissue. **b** Immunofluorescent staining (collagen in green and DAPI in blue) of human cortical ovarian tissue. (Periodic Acid-Schiff (PAS) stain is mainly used to detect carbohydrates in tissues; 4′,6-diamidino-2-phenylindole (DAPI) is a fluorescent dye that can bind to DNA, which is mainly used for cell staining). Reproduced with permission from [48]

Human ovarian stromal cells and pre-antral follicles could be reseeded to the scaffolds and cultured in vitro and transplanted subcutaneously to immunodeficient mice. As a result, human ovarian stromal cells were observed to recellularize the scaffolds, and about 39% of pre-antral follicles grew into antral stages without malignancy [48]. It is speculated that all of these dECM models act as a biologic scaffold by assisting epithelialization, neovascularization, and fibroblast infiltration, however, there is limited research into the exact mechanisms, and supporting data is still needed.

The biggest practical drawback of microfluidic hydrogel encapsulation technology is the limited number of follicle cells encapsulated. When applied to large animals and humans, an ideal biological scaffold needs to carry a large number of follicular cells while achieving the vascularization, infiltration of nutrients, discharge of follicles, and secretion of hormones. Emerging additive manufacturing techniques such as 3D printing microporous hydrogel scaffolds (Fig. 4), which serve as pore architecture to encapsulate ovary follicles, are alternative approaches that have facilitated the development of bioengineering. Controlled microporous architectures can be constructed by 3D printing thermally regulated crosslinked gelatin, where interestingly 60° angle scaffolds were the most efficient for cell growth and maturation When transplanted to surgically sterilized mice, the artificial 3D printed follicle-seeded scaffolds became highly vascularized and started to ovulate and secrete hormones. Next, the healthy delivery of mice was reported following natural mating [77]. Moreover, Jakus AE et al. elaborated that the dECM "bioink" from bovine ovarian is usable in 3D printing (Fig. 5), indicating the 3D printing technology might be promising in future human fertility reservation applications [116].

3.2 Uterine tissue engineering using collagen-based biomaterials

The treatment of infertility has been partially resolved with the emergence of IVF technology. However, IVF can only resolve infertility due to fallopian tube and ovulation factors. Surrogacy on the other hand, which is illegal in most countries due to ethical controversy, is currently the only option to resolve absolute uterine infertility (absent or non-functional uterus), which has a prevalence of 3–5% in all women [117].

Owing to the rapid development of materials in recent years, the exploration of a tissue-engineered artificial uterus offers some hope to patients suffering from uterine infertility. Research on engineering uterine tissue is generally in the exploratory stage and mainly applies recellularized uterine dECM scaffolds in animal transplantation models. The dECM scaffold is produced by perfusing Triton X-100 and Sodium dodecyl sulfate (SDS)/Dimethyl sulfoxide (DMSO) into the uterus. Immunofluorescence staining of the dECM scaffold shows that the collagen content remains intact after this process [56], after which recellularization procedures can be achieved by injecting stem cells into dECM scaffolds. In a pilot study, the uterine epithelial cells were artificially migrated into a dECM scaffold. The modified scaffold was transplanted into an artificially defective murine uterus. An intact epithelial layer formed and the migration and regeneration of myometrial and stroma cells were observed sequentially,

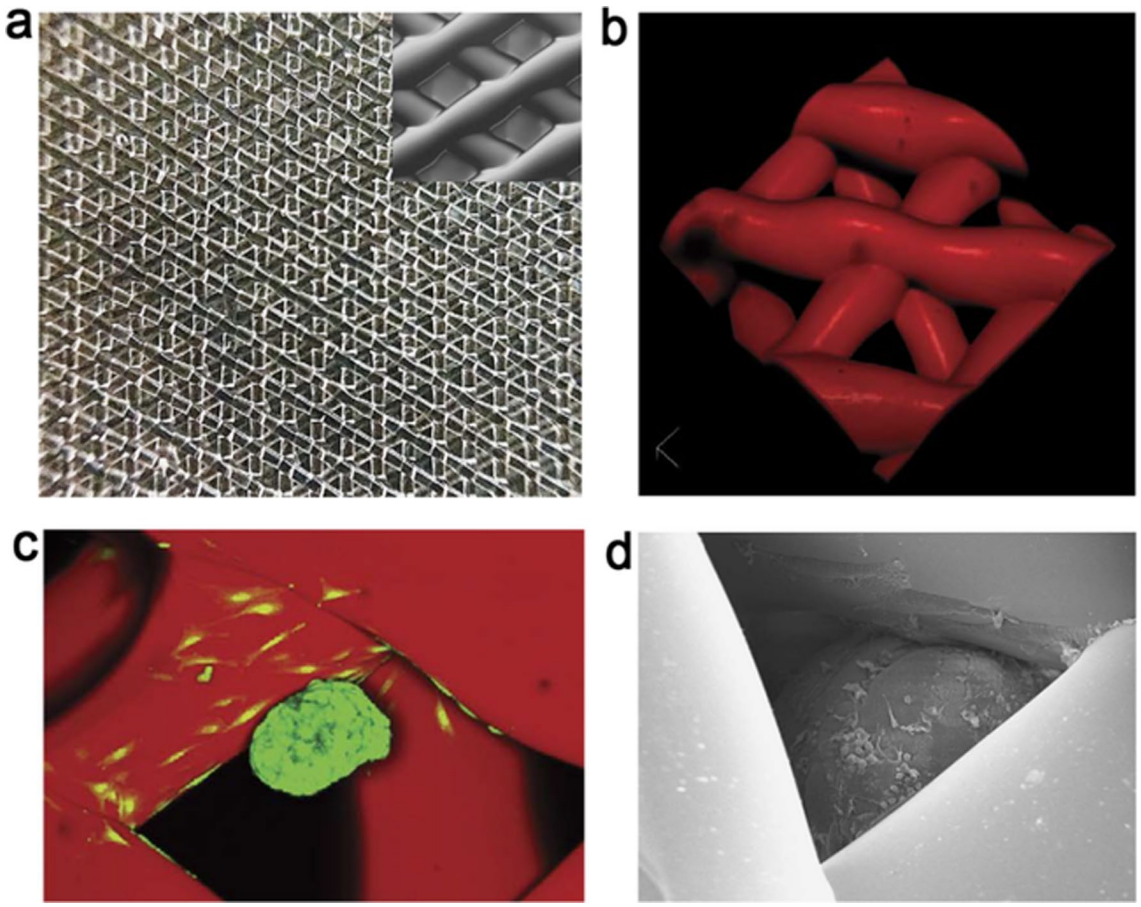

Fig. 4 Ovarian follicles cultured in 3D printed microporous gelatin scaffolds. **a** Macroscopic view of 3D printed microporous gelatin five-layered scaffolds printed with a 100 mm nozzle. **b** 3D reconstructions of a confocal fluorescence image of 60° angle gelatin scaffolds. **c** Confocal fluorescence image of follicles seeded in pores after 2 days of culture. **d** Electron micrograph of an ovarian follicle wedged underneath 60° angle gelatin scaffolds after 2 days of culture. Reproduced with permission from [77]

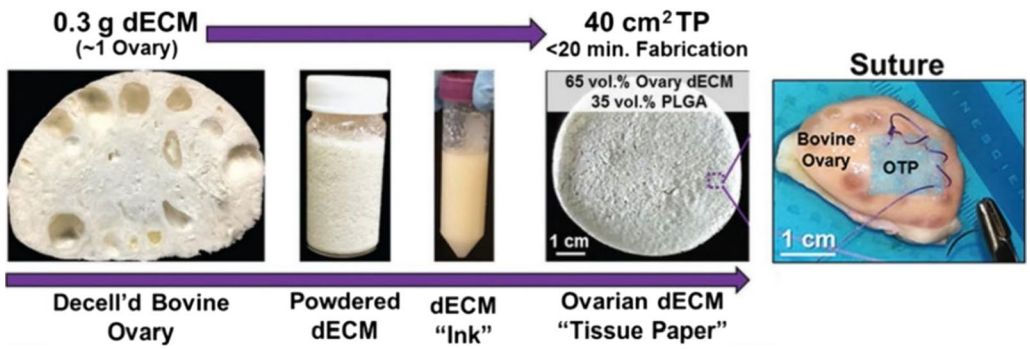

Fig. 5 Re-transplantation of "tissue paper" made from bovine ovarian dECM tissue. Reproduced with permission from [116]

indicating that the application of the dECM was a promising strategy for the regeneration of epithelium and myometrium in the uterus [66]. Pregnancy was even reported in another study that transplanted dECM scaffolds recellularized with endometrial and myometrial primary cells to repair native rat uterine tissue defects in vivo [55]. Similarly, collagen scaffolds layered with human umbilical cord-derived mesenchymal stem cells have been used

to reconstruct endometrium and preserve fertility in an induced murine uterine defect model [13]. In addition, a whole porcine uterus has been decellularized while maintaining the vascular network and preserving the dECM (Fig. 6). These researchers also successfully recellularized the small acellular disk scaffolds with human side population stem cells [56].

3.3 Cervicovaginal tissue engineering using collagen-based biomaterials

The vaginal matrix is composed of various proteins such as collagen, microfibrils, and elastin. Treatment of congenital absence of the vagina, vaginal deformity, and acquired vaginal trauma have been challenging owing to the lack of compatible and useful biomaterials. Autologous tissues such as bladder mucosa and full-thickness skin grafts have been used in vaginal reconstruction. However, extra trauma caused by obtaining autologous tissue is a significant issue for patients. The development of artificial materials such as engineered acellular intestinal submucosa segments [12], collagen, or dECM layered scaffolds [109] provides promising solutions. Engineered scaffold with the commercial name ADM (QingYuan WeiYe Biotech, Beijing, China) that is layered with critical dECM components containing collagen, elastin, and proteoglycans has been applied to 53 patients with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, a disease of congenital absence of the uterus and vagina. As a result, follow-up showed near-normal sexual function and satisfaction for all patients [103]. Acellular porcine small intestinal submucosa (SIS), which is primarily composed of non-crosslinked collagen, glycosaminoglycans, proteoglycans, and glycoproteins [118], has also been successfully applied to 8 patients with cervicovaginal agenesis or dysgenesis and 2 patients with MRKH syndrome [104, 105]. The collagen-based materials showed superior biocompatibility and did not produce immunologic rejection during the application. In addition, it spared patients from the additional trauma of traditional reconstruction through autologous tissues vaginoplasty. Moreover, collagen-based electrospun materials have been applied to tissue engineering and wound healing. Electrospinning of type I collagen scaffolds leads to similar materials to native dermal ECM that are capable of supporting angiogenesis and epithelialization, and show greater resistance to tissue contraction, which makes them promising for vaginal reconstruction [119].

3.4 Pelvic reconstruction using collagen-based biomaterials

It is estimated that more than 25% of women suffer from POP, a disease defined as the herniation or descent of pelvic organs into the vagina, of which the estimated lifetime risk of surgery is about 19% [120]. Synthetic polypropylene (PP) meshes have been widely applied in POP reconstructive surgery. However, this risks adverse events such as foreign body tissue response, chronic pain, tissue contracture, and mesh exposure. To minimize adverse effects, numerous studies have designed collagen coatings to modify PP mesh. For example, less erosion and inflammation were reported when coating the PP mesh with acellular porcine collagen, which could decrease mesh tissue adhesion to the surgical wound, prevent severe initial inflammatory response, and diminish the risk of chronic pain and mesh exposure [109, 110]. In addition, ECM coating can be applied to improve the biocompatibility of mesh owing to its degradable properties, which facilitate wound tissue remodeling and tissue formation rather than tissue fibrosis [111]. In

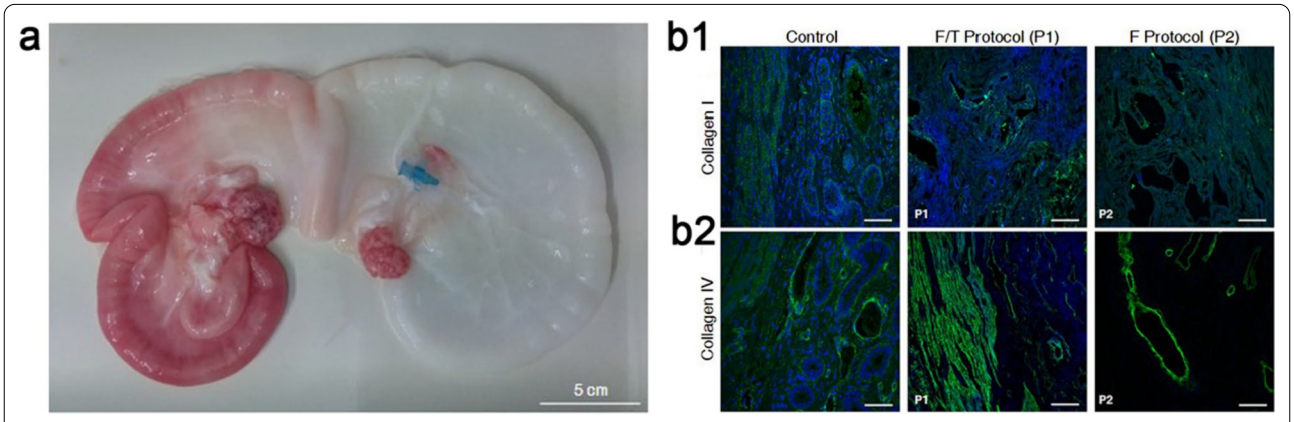

Fig. 6 dECM of porcine uterus. **a** Macroscopic picture of porcine uterine horns after decellularization (DC). **b1, b2** Immunofluorescence staining of collagen I (green signal of **b1**) and collagen IV (green signal of **b2**) after DC. (Control: uterus before DC. P1: freeze/thawed samples after DC. P2: Fresh samples after DC). Reproduced with permission from [56]

addition, PP materials coated with collagen type I and III were reported to facilitate the adhesion and proliferation of human urothelial cells, which is promising in the application of urethral reconstruction [121]. However, mesh erosion is still a difficult problem since PP mesh is non-degradable. Therefore, a biodegradable, more biocompatible biomaterial is in urgent need. Recently, an electrospun polycaprolactone resorbable mesh showed no erosion in an ovine model [122]. Inspired by the successful application of collagen-based electrospun materials in skin tissue and musculoskeletal engineering, we hypothesize that collagen-based electrospinning is promising for improving biocompatibility and biodegradability in pelvic reconstruction.

3.5 Regenerative medicine using placenta ECM

The placenta contains an abundance of ECM and is relatively easy to acquire as stem/progenitor cells are discarded after delivery. It is assumed that placenta ECM represents a valuable resource for regenerative medicine, especially for tissue engineering, because of its ample bioactive molecules essential for regeneration [102]. However, the application of placental ECM is still in its infancy.

4 Discussion

Reproductive medicine, especially human fertility preservation strategies and reproductive organ regeneration, has gathered increasing attention because of the aging populations seen globally. Collagen, a renewable resource with a wide range of sources, provides an ideal choice for solving clinical problems in regenerative medicine. The principles of leather manufacturing can inspire resolving the current challenges in the engineering of collagen-based regenerative materials. Moreover, the chemistry of leather tanning may also provide a guideline in the fundamental design of regenerative materials to better meet clinical requirements in regenerative medicine.

4.1 Tanning chemistry-based inspiration

The mechanism of leather tanning can inspire the engineering of materials with strong mechanical properties. One of the most serious shortcomings of collagen-based biomaterials is that the weak mechanical properties result in the loss of the collagen porous structure. This property makes it impossible for current collagen-based materials to truly replace the ECM to support cell growth and other functions. The leather manufacturing process is the process of enhancing the mechanical properties of leather and maintaining the collagen structure. This suggests that through a similar process to leather manufacturing, the mechanical properties of collagen could be improved while ensuring the physiological activity to ensure that collagen-based biomaterials can better meet the needs of regenerative medicine.

In addition, the metal-tannin combination process can impart multiple functions to biomaterials due to the coordination property of polyphenols (tannins). Metal-phenol networks (MPNs) have been widely used in biomedical research, and have shown great application potential in the fields of drug-controlled release and cell interface engineering. The shortcomings of cytokines, DNA drugs, and RNA drugs are that they are easily degraded and inactivated, which limit their application in the field of reproduction. Therefore, designing specific metal polyphenol-containing collagen-based biomaterials according to clinical needs is expected to further expand the application range of collagen materials in the field of reproductive medicine.

4.2 Collagen-based soft electronic materials

Collagen-based biomaterials show unique advantages, such as superior biocompatibility and biodegradability, potentially useful for preparing soft electronic materials. Health monitoring has a wide range of applications in reproductive medicine. Collagen-based soft electronic materials, therefore, have great application prospects in the field of health monitoring.

4.3 Fertility preservation strategies and hormone replacement therapy (HRT) perspectives

Re-transplantation after cryopreservation of ovarian tissue is the only option to preserve fertility in prepubertal females and patients who require immediate cancer treatment. However, the initial tissue ischemia after re-transplantation is also a problem that plagues physicians. Collagen-based tissue engineering provides a new perspective in aiding the initial revascularization process and the isolation of malignant cells in ovary re-transplantation. Artificial collagen-based biomaterials that encapsulate ovarian follicles with hormone secretion functions are expected to serve as a more precise HRT, which is expected to be much closer to the natural female physiological state and with fewer side effects.

4.4 Tissue regeneration, organ reconstruction, and artificial uterus perspectives

One of the most promising new frontiers in current medicine is regenerative medicine. It is hoped that in the future, the development of engineered tissue can provide fewer adverse reactions such as rejection, tissue contracture, and scar hyperplasia. Moreover, the regeneration of nerve cells in engineered tissue is promising for regaining sexual sensation for patients suffering from congenital absence of the vagina, vaginal deformity, and acquired vaginal trauma. Also, a

tissue-engineered artificial uterus provides hope to patients suffering from uterine infertility.

5 Conclusion

In this review, we introduced the collagen-based materials used in reproductive medicine, including collagen hydrogel scaffolds, decellularized ECM, and collagen-based bioinks. Additionally, five current applications of collagen-based biomaterials (i.e., ovarian tissue engineering, uterine tissue engineering, cervicovaginal tissue engineering, pelvic reconstruction, and placenta ECM) were reviewed comprehensively. Finally, we discussed the relationship between the exploration of collagen-based materials used in reproductive medicine and the leather industry. This review will hopefully provide integrated knowledge and interesting perspectives for researchers committed to conducting cutting-edge studies and promoting the development of artificial materials in reproductive medicine.

Abbreviations

ECM: Extracellular matrix; dECM: Decellularized ECM; IVF: In vitro fertilization; ICSI: Intracytoplasmic sperm injection; IVM: In vitro maturation; Gly: Glycine; Pro: Proline; Hyp: Hydroxyproline; 3D: Three-dimensional; 2D: Two-dimensional; Pue@GelMA: Pue-loaded gelatin methacrylate; POP: Pelvic organ prolapse; CDI: Carbodiimide; HMDC: Hexamethylene diamine carbamate; GP: Genipin; PC: Proanthocyanins; NDGA: Nordihydroguaiaretic acid; iPSC: Induced pluripotent stem cell; MSC:: Mesenchymal stem cell; AVM:: Acellular vagina matrix; Col:: Collagen; Alg:: Alginate; O-alg:: Oxidized-alginate; PAS:: Periodic acid-Schiff; DAPI:: 4′,6-Diamidino-2-phenylindole; DC:: Decellularization; MRKH:: Mayer-Rokitansky-Küster-Hauser; SIS:y: Small intestinal submucosa; PP:: Polypropylene; VEGF:: Vascular endothelial growth factor; MPN:: Metal-phenol network; HRT:: Hormone replacement therapy.

Acknowledgements

We thank Meifeng Li for the useful discussion.

Authors' contributions

YZ, JG, and LQ made substantial contributions to the conception and design of this review. HC, LX, and GG wrote the manuscript. JP and XW participated in the design of figures in this review. All authors read and approved the final manuscript.

Funding

The work in the L.Q. laboratory was financially supported by the Sichuan Science and Technology Program (L.Q., Grant No. 2020YFS0127). The work in the Y.Z. laboratory was financially supported by the Research project of Science & Technology Department of Sichuan Province (Y.Z., Grant No. 2021YJ0416), project of Chengdu Science and Technology Bureau, (Y.Z., Grant No. 2021-YF05-02110-SN) National Natural Science Foundation of China (Y.Z., Grant No. 82001496), China Postdoctoral Science Foundation (Y.Z., Grant No. 2020M680149, 2020T130087ZX). The work in the J.G. laboratory was financially supported by the National Global Talents Recruitment Program (J.G.), National Natural Science Foundation of China (22178233), Talents Program of Sichuan Province, Double First Class University Plan of Sichuan University, State Key Laboratory of Polymer Materials Engineering (J.G., Grant No. sklpme 2020-3-01).

Availability of data and materials

The datasets analyzed in this review are available as quoted and listed in the "References" section which have been specified in the article.

Declarations

Competing interests

The authors declare no competing interests.

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Received: 28 June 2021 Accepted: 10 November 2021
Published online: 15 January 2022

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