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Cellulose as a sustainable scaffold material in cultivated meat production

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ABSTRACT

The rapid progress in cultivated meat research has engendered considerable attention towards the edible scaffolding biomaterials employed in the production. Cellulose has the advantages in availability, edibility, animal-free origin, etc., which show its potential in wide fields. This review begins by presenting the fundamental physical and chemical properties of cellulose from different sources, including plant and bacterial cellulose. Subsequently, we summarize the application of cellulose especially in cultivated meat and tissue engineering. Furthermore, we explore various methods for preparing cellulose-based scaffolds for cultivated meat, encompassing five specific structural variations. In the end, associated with utilizing cellulose in cultivated meat production, we address several primary challenges surrounding to cell adhesion, scaling up, processibility and mechanical properties, and provide potential innovations. This review underscores the potential of cellulose as a versatile biomaterial in the cultivated meat industry and provides insight into addressing critical challenges for its integration.

1. Introduction

1.1. Cultivated meat

The continuous growth of the world population and the improvement of per capita economic income in some countries have stimulated the rising demand for meat consumption (Rauw et al., 2020). While in recent years, the spread of the COVID-19 pandemic (Nendissa et al., 2021) and animal diseases (Clemmons et al. 2021) (e.g., African swine fever, ASF, and highly pathogenic avian influenza, HPAI) have impacted traditional meat supply. Therefore, the increasing demand for meat consumption cannot be met by traditional meat production. Besides, there are series problems and limitations in the meat production based on traditional animal husbandry, such as environment (Hong et al., 2021; Ibidhi and Ben Salem 2020; Xu et al., 2021), food safety (Guo et al., 2022; Patel et al., 2020; Qaid and Abdoun 2022), production efficiency (Gorlov et al., 2020; Jiang et al., 2020; Smith and Myers 2022), and animal welfare (Sinclair et al., 2023). Based on these, more and more research institutions and industry enterprises have begun to pay attention to cultivated meat, in order to fill the supply gap of traditional slaughter meat, and create new proteins with a tunable composition and nutrition that are environmentally friendly, have low-carbon footprints, and are produced efficiently.

Cultivated meat is meat substitute produced by *in-vitro* proliferation and differentiation of cells extracted from terrestrial animals (e.g., chicken, cattle, sheep, pig) and marine animals (e.g., fish, shrimp, crab, lobster) based on stem cell biology and tissue engineering (Post et al., 2020; Rubio et al. 2020). It's also known as cell-based meat, cultured meat, cellular meat, *in-vitro* meat, etc. Since cultivated meat is clean, safe, nutrition-tunable, and in accordance with animal welfare, it is also referred to as clean meat, customizable meat, animal-free meat, new meat, lab-grown meat, etc.

The production process of cultivated meat is as follows: (1) Cell harvesting: cells are extracted from animals and optimized to create a pool of high-quality cell lines suitable for large-scale proliferation. (2) Mass production of cells, which are grown in bioreactor and added to a

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medium to provide growth conditions that encourage large-scale, low-cost proliferation. (3) The organization and production of cells: the use of scaffolding technology or 3D printing cells to form the three-dimensional structure of meat, through food processing, from the flavor, taste, nutrition innovation, turn cellular raw materials into end products.

Above production processes of cultivated meat include four key aspects: cells, culture media, scaffolding biomaterials, and bioreactors (Rubio et al. 2020). Briefly, a small amount of muscle and fat cells are isolated from tissues or live animals, whereafter expended and differentiated successively in bioreactors. During this *in-vitro* culture, culture media provide essential nutrients and growth factors, scaffolding biomaterials ensure efficient transport of oxygen, nutrients, and waste products (Bomkamp et al., 2022), to elicit desired cellular behaviors like attachment, hypertrophy, proliferation, and differentiation (O'Neill et al., 2021). One challenge of cultivated meat production is high-density expansion of anchorage-independent cells. Another challenge is mimicking the texture of real meat and forming large whole-cut meat, which are closely related to tissue maturation. To facilitate these, scaffolding biomaterials play a crucial role.

1.2. Scaffolding biomaterials

Scaffolding biomaterials appear early in tissue engineering, they provide a structural framework that resembles the fibrous protein component of the extracellular matrix (ECM) (Jenkins and Little 2019). The ideal cultivated meat biomaterial should fulfil the following criteria (Bodiou et al. 2020; Bomkamp et al., 2022): (1) Promote favorable cell adhesion and growth, which is the essential requirement; (2) Be separable, biodegradable, or edible; edible biomaterials are the ideal choice as they simplify the production process of cultivated meat, aiding in regulating the texture and taste of cultivated meat products; (3) Provide nutritional value or dietary function; (4) Possess good thermal stability, in order to prevent decomposition of the biomaterial after cooking, resulting in drastic alteration of the structure and mechanical properties of cultivated meat; (5) Be commercially viable and able to be produced on a large scale at a reasonable cost.

In cultivated meat, the existing raw materials for scaffolding biomaterials mainly focus on collagen/gelatin (Ahmad et al., 2021; Enrione et al., 2017; Gribova et al., 2016; MacQueen et al., 2019; Wang et al., 2011), soy protein (Ben-Arye et al., 2020), alginate (Apsite et al., 2020; Fukushima et al., 2013), chitin/chitosan (Park et al., 2021; Rubio et al., 2019), agarose (Jaques et al., 2021; Park et al., 2021), cellulose (Park et al., 2021), hyaluronic acid (Chen et al., 2021), and decellularized plants (Cheng et al., 2020; Jones et al. 2021; Modulevsky et al., 2014). Animal proteins such as collagen/gelatin have the best affinity for cells, but they come from animals or expensive recombinant proteins. Plant proteins such as soy protein have excellent cytocompatibility and are non-animal derived materials, but they often have mechanical property defects after being made into biomaterials, so they are often compounded with other materials. Non-animal derived polysaccharides such as chitin/chitosan, agarose, cellulose, and hyaluronic acid have higher mechanical strength, but their biocompatibility is not as good as animal proteins, so they usually need chemical modification or surface pattern modification. Decellularized plant tissue is chemically similar to cellulose, but it retains the complex structure of the plant and facilitates cell adhesion, proliferation, or regular cell arrangement and differentiation.

Cellulose is the most abundant natural polymer material, with good biocompatibility and excellent mechanical properties, non-toxic, renewable, in nature can be biodegradable, and it is easy to carry out appropriate chemical surface modification. Besides, cellulose has not been employed much as scaffolding biomaterial in cultivated meat despite the advantages mentioned above even though it has been extensively used in other biomedical applications such as tissue engineering, wound healing, drug delivery, and cancer treatment.

In this review, the structure and basic physicochemical properties of cellulose were introduced, the preparation methods of cellulose-based biomaterials were reviewed, and the application challenges and coping strategies of cellulose in cultivated meat biomaterials were summarized and prospected, in order to provide a reference for the development and application of cellulose-based biomaterials in the field of cultivated meat.

2. Sources and properties of cellulose

Cellulose is an unbranched linear polymer formed by β-D-pyran glucose units linked by β-glycosidic bonds at the C_1, C_4 positions, with the molecular formula $(C_6H_{10}O_5)_n$. Cellulose has both crystalline regions and amorphous regions, with the former accounting for a large proportion and causing low accessibility of cellulose, so the crystalline structure needs to be disrupted to make cellulose easier to react. From the chemical structure, cellulose is rich in hydroxyl groups. Specifically, the C_1 at one glucose end group of the cellulose chain has a hydroxyl group, as a recessive aldehyde group, which has high reactivity under certain conditions. Each of the glucose groups in the middle has a secondary alcohol hydroxyl group at C_2 and C_3, and a more reactive primary alcohol hydroxyl group at C_6. The unique chemical structure of cellulose provides a conformational basis for its degradation, esterification, etherification, and graft copolymerization. Meanwhile, the hydroxyl groups on the surface of cellulose are negatively charged and have the conditions to form hydrogen bonds with other substances. Therefore, cellulose is expected to be designed as a biomaterial with multiple functions through various modification methods.

2.1. Plant cellulose

Cellulose is the main component of plant cell walls, accompanied by hemicellulose and lignin to support and protect plant cells. Common isolation methods of plant cellulose include acid hydrolysis and mechanical defibrillation. According to size and morphology, the extracted cellulose includes two representative types: cellulose nanocrystals (CNC; or cellulose nanowiskers, CNW; or nanocrystalline cellulose, NCC) and cellulose nanofibers (cellulose nanofibers, CNF; or nanofibrillated cellulose, NFC) (He et al., 2021; Sharif et al. 2020). CNC is rod-like cellulose with an aspect ratio of 10–100, which is mainly prepared by acid hydrolysis. Its length is 50–500 nm and its diameter is 3–20 nm. CNF is filamentous cellulose with an aspect ratio greater than 100, mainly prepared by mechanical defibrillation, which can be supplemented by chemical or enzymatic pretreatment, with 500-10,000 nm in length and less than 100 nm in diameter (He et al., 2021).

The degree of polymerization (DP) of cellulose shows great variation depending on the plant sources, separation methods, and measurement methods. The DP of cellulose of agricultural residue (e.g., bagasse, wheat straw) is approximately 1000, while that of wood is about 4000–5000, and for cotton is approximately 10000 (Hallac and Ragauskas 2011). In addition, the crystallinity of plant cellulose is about 40–60%.

2.2. Bacterial cellulose

In addition to plants, cellulose can also be derived from microorganisms, i.e., bacterial cellulose (BC). BC naturally has high purity, high crystallinity (70–80%), high DP (up to 8000), high moisture content (99%), and good biocompatibility, and can be produced in large-scale, so it has attracted more and more attention in food, tissue engineering, and other fields. The earliest discovered and most typical microorganism that can produce BC is *Komagataeibacter xylinus* (*K. xylinus*, which was once belonged to *Acetobacter* and *Gluconacetobacter* genus successively) (Yamada et al., 2012), which is also the model strain for studying BC synthesis. Many of the microorganisms that can generate BC are pathogenic, or not applied in the food field, or have low yield and efficiency in BC synthesis, so bacteria of the *Acetobacteraceae* family are

often selected for fermentation culture in commercial BC production, and companies often have their own screened high-yielding strains.

BC obtained in static culture is a lamellar gel mat formed at the gas-liquid interface of the culture system, which is translucent milky white after cleaning. Under dynamic culture conditions such as agitation and oscillation, BC can be spherical, ellipsoidal, stellate, fibrous suspensions, pellets, or irregular masses (Wang et al. 2019). BC has a 3D fibrous network structure under an electron microscope, and the fiber gap is in the nanometer scale (about 100–300 nm in diameter (Hutchens et al., 2006)). This gap is too small for animal cells to enter and grow inside the material, so the BC used for cultivated meat biomaterials must undergo structural adjustment. As BC is a product secreted by microorganisms in the motion state, its structure is directly related to the motion mode of microorganisms, so different structures of BC can be obtained by limiting the moving space or direction of microorganisms, which can be achieved by controlling microbial fermentation conditions and bioreactor structure. For example, vascular tubular BC can be obtained with central or/and external oxygen-permeable tubular bioreactors (Bao et al., 2020).

2.3. Modified cellulose

The water-soluble modification of cellulose makes it easier to process and shape, and affects other properties such as the viscosity of the cellulose solution, thus forming biomaterials with different rheological properties ranging from bioinks to hydrogels. Surface charge modification also helps cellulose to enhance cell adhesion, but since existing charge-modified cellulose (positively charged cellulose such as quaternary ammonium cellulose; strongly negatively charged cellulose such as sulfonic acid cellulose, cellulose acetate) are beyond the scope of being approved for food additives in many regions, charge-modified cellulose will not be discussed further here. Water-soluble modified cellulose mainly includes the following.

(1) Carboxymethyl cellulose (CMC) is obtained by replacing the hydrogen atoms on part of the hydroxyl groups with anionic carboxymethyl groups (-CH_2COOH) on the basis of the original cellulose structure. The provider of the carboxymethyl groups can be chloroacetic acid (Barkhordari et al. 2014), etc. It has the characteristics of low crystalline index of fibers, non-toxicity, pH sensitivity, hydrophilicity and water solubility, high stability of dispersion, gelling property, biocompatibility, biodegradability, good film-forming ability, easy availability, high viscosity, low price, etc., making it an ideal raw material for preparing hydrogels (Javanbakht et al., 2020; Liu et al., 2019; Rezaei et al. 2015). In the food field, CMC can be used as thickener, film former and texture ingredient for ice cream, pies, sauces, beverages and other foods (Saha et al., 2013). Additionally, it has a wide range of applications in tissue engineering, wound dressings, drug delivery, and other areas (Zohuriaan-Mehr and Kabiri 2008).
(2) Other cellulose derivatives such as hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC) (Kim et al., 2016), and ethyl cellulose (EC) can be obtained by replacing some of the hydroxyl groups in natural cellulose with hydroxyethyl groups, methyl groups, etc. This transformation endows the modified cellulose with water solubility and hydrophobicity in specific temperature ranges (Chang and Zhang 2011). At high temperatures, the adjacent groups form a physical gel (i.e., gel state) by van der Waals forces; at low temperatures, these van der Waals forces of lower energy are released and the above modified cellulose is dissolved in water again (i.e., sol state). As a result, these cellulose derivatives can achieve thermally reversible gelation (i.e., sol-gel transition).

2.4. Advantages of cellulose for cultivated meat biomaterials

Cellulose has the following key advantages for cultivated meat biomaterials.

(1) Abundant and easily obtainable. It is the most abundant natural polymer in the world, widely exists in the cell walls of plants, and can also be obtained by microorganisms and even individual animals.
(2) Edible and healthy. It is "generally recognized as safe" (GRAS) by the US Food and Drug Administration (FDA), and is also allowed to be added to food in some other regions including the European Union, China, and Japan. Cellulose is dietary fiber with a high proportion in many unrefined grains, vegetables, fruits, and other natural foods. Although it cannot be digested and absorbed by humans, it can effectively promote gastrointestinal peristalsis and is beneficial to health. In addition to plants, cellulose can also be derived from microbial fermentation, namely BC. The main ingredient of "Nata de Coco" is BC, which has become popular in many countries in recent years. It is added to beverages, desserts, or eaten directly.
(3) Capable of achieving large-scale production. The production process of cellulose has long formed a mature system, and has successfully achieved industrial production (Zhong 2020).
(4) White or nearly white in color and tasteless, making cellulose easy to adjust color and flavor, so as to imitate the sensory effect of meat.

3. Application of cellulose in cultivated meat and tissue engineering

The nanofiber network of cellulose is structurally similar to collagen in the natural ECM. As a promising scaffold material, cellulose has been used in various fields in cultivated meat and tissue engineering.

3.1. Application of cellulose in cultivated meat and muscle tissue engineering

The commercially available unmodified BC product from Cass Materials was tested the suitability for murine myoblast attachment, proliferation, and differentiation (Fig. 1A) (Rybchyn et al., 2021). The retention rate of myoblast cells appeared low, while the product provided effective surface parameters for the formation of anchor points to form mature myotubes. Cellulose (BC and CNF) was prepared into films without toxic cross-linking or stabilizing agents, and compared with other naturally non-animal derived polysaccharides and proteins (Fig. 1B) (Xiang et al., 2022). These films were investigated for support of the adhesion, proliferation and differentiation of murine and bovine myoblasts, while polysaccharide-based films showed better cell adhesion than the protein-based films.

To enhance cell adhesion on the cellulose surface, a strategy was employed involving the coating of cellulose nanofiber films with a fusion protein comprised of a cellulose binding domain (CBD) protein and the cell-adhesion peptide motif RGD (Cohen 2022). Bovine satellite cells cultured within the system showed enhanced attachment. Other modifiers and methods were also used to promote cell behaviors on cellulose. Cellulose acetate (CA) nanofibers associated or not with a food-dye (bioactive annatto extract) were fabricated into porous scaffolds with mean fiber diameter of 420 nm (Fig. 1C) (Santos et al., 2023). While CA scaffold favored C2C12 myoblast differentiation, the annatto-loaded CA scaffold favored a proliferative state of these cells. A polysaccharide film-based platform consisting of CMC, chitosan and agarose was developed (Fig. 1D) (Park et al., 2021). C-phycocyanin (C-PC), a substitute for animal-derived serum, was incorporated into the inner porous structure of the platform, to improve myoblast proliferation in a serum-reduced environment during long-term culture.

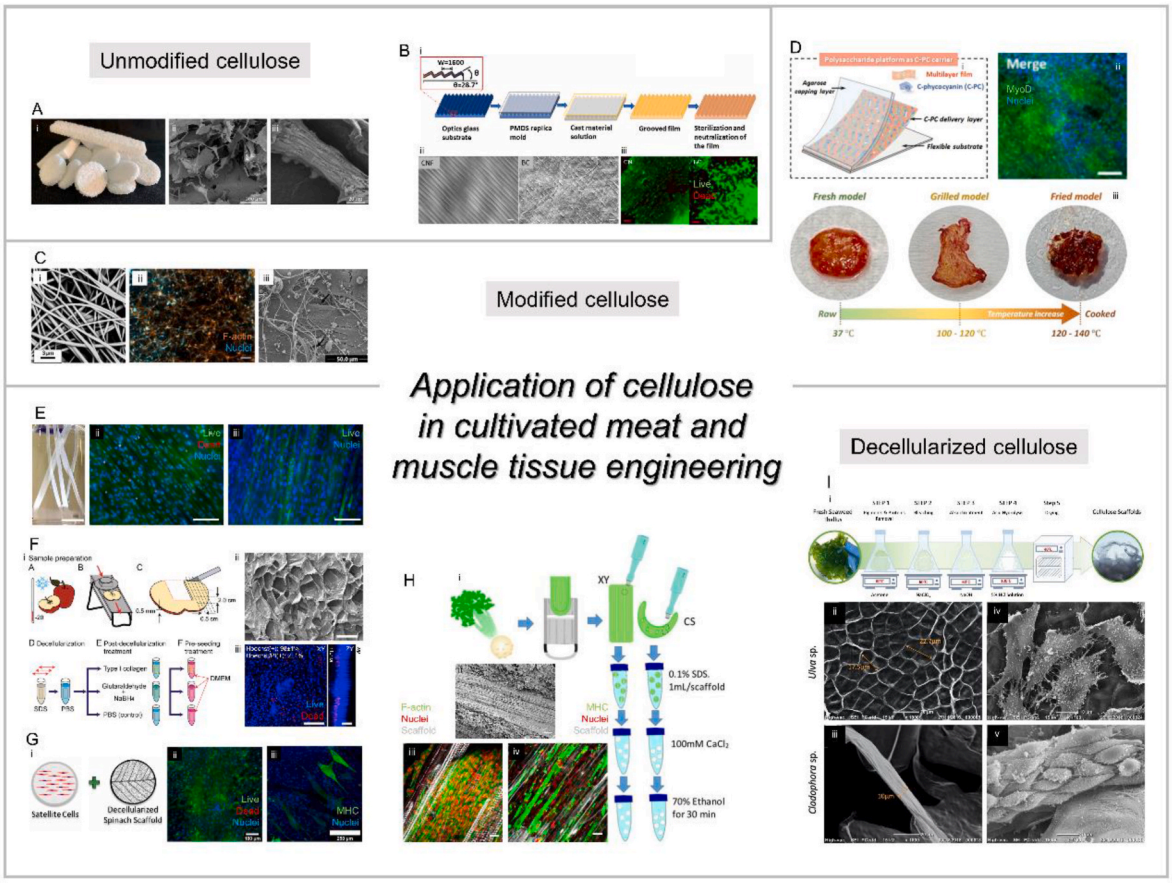

Fig. 1. Highlighted examples of cellulose-based biomaterials applied in cultivated meat and muscle tissue engineering. A) i) Bacterial nanocellulose scaffolds (BNS) with ii) pore details. iii) Differentiated C2C12s after 1 month in 2% v/v HS, showing typical cylindrical myotube structures within the BNS matrix. Adapted with permission (Rybchyn et al., 2021). Copyright 2021, American Chemical Society. B) ii) CNF and BC films with surface microstructures were prepared by i) casting solutions onto patterned PDMS substrate (2 μm scale bars). iii) C2C12s cultured on CNF and BC films on day 6 (100 μm scale bars). Reproduced under the terms of the Creative Commons Attribution (CC BY) license (Xiang et al., 2022). Copyright 2022, The Authors. Published by Elsevier. C) i) CA annatto (CA@A) nanofibers. C2C12s cultured onto nanofibers after 7 days, ii) thinner and randomly distributed than those onto the CA@A ones (50 μm scale bars), iii-iv) arrows indicate cell-nanofiber adhesion points. Reproduced under the terms of the Creative Commons Attribution (CC BY) license (Santos et al., 2023). Copyright 2023, The Authors. Published by Frontiers. D) i) Porous CMC-chitosan-agarose platform incorporating C-PC with ii) crosslinking structure. iii) C2C12 monolayer-cell sheet formed on the platform showed cell proliferation for 10 days even in FBS-reduced environment (50 μm scale bar). iv) Cell sheet-based cultured meat model before and after cooking. Reproduced under the terms of the Creative Commons Attribution (CC BY) license (Park et al., 2021). Copyright 2021, The Authors. Published by American Chemical Society. E) i) Decellularized grass (1 cm scale bar). C2C12s ii) cultured for 7 days and iii) differentiated for 7 days showed cell alignment and myotube formation on the scaffold (100 μm scale bars). Reproduced under the terms of the Creative Commons Attribution (CC BY) license (Campuzano et al. 2020). Copyright 2023, The Authors. Published by Wiley. F) i) Preparation of decellularized apple scaffolds with ii) pore details (200 μm scale bar). iii) C2C12s have proliferated throughout the structure during the 12-week culture (Scale bars: 200 μm for XY and 100 μm for ZY). Reproduced under the terms of the Creative Commons Attribution (CC BY) license (Modulevsky et al., 2014). Copyright 2014, The Authors. Published by PLOS. G) i) Decellularized spinach scaffolds seeded with BSCs supports ii) cell viability and iii) differentiation within 14 days. Reproduced under the terms of the Creative Commons Attribution (CC BY) license (Jones et al. 2021). Copyright 2021, The Authors. Published by Elsevier. H) i) Preparation of decellularized celery scaffolds with ii) microscale grooves of vascular bundles (200 μm Scale bar). iii) After 10 days of culture, C2C12s maintained alignment on the scaffold (25 μm Scale bar). iv) After 5 days of differentiation, aligned myotubes formed (100 μm Scale bar). Reproduced under the terms of the Creative Commons Attribution (CC BY) license (Allan et al. 2021). Copyright 2020, The Authors. Published by bioRxiv. I) i) Preparation and ii-iii) two structures of decellularized seaweed cellulose scaffolds. iv-v) NIH-3T3s revealed cell growth and attachments onto the *Ulva* sp. porous matrix and *Cladophora* sp. fibrous matrix. Adapted with permission (Bar-Shai et al., 2021). Copyright 2023, Springer Nature.

Moreover, various cellulose-rich plants including apple, spinach, celery, scallion and amenity grass have been directly processed into biomaterials using decellularization (Fig. 1E–H) (Allan et al. 2021; Campuzano et al. 2020; Jones et al. 2021; Modulevsky et al., 2014). The obtained cellulose with natural unique structures (e.g. alignment of vascular bundles) are suitable for cultivated meat application. Interestingly, marine macroalgae species can also be the resources of decellularized biomaterials. *Ulva* sp. and *Cladophora* sp., with porous and fibrous structures respectively, were decellularized to fabricate seaweed cellulose-based scaffolds for *in-vitro* mammalian cell growth (Fig. 1I) (Bar-Shai et al., 2021). On both scaffolds, fibroblasts showed high viability for up to 40 days in culture.

3.2. Application of cellulose in vessel tissue engineering

Due to its non-toxic, high purity, good tensile strength and plasticity, and ultrafine fiber network, BC has high application potential as a tubular scaffold material (Zang et al., 2015). Meanwhile, recent studies have shown that BC nanofibers are a potential material for preventing blood clots (Choi et al., 2022). In addition, cellulose and its derivatives have good biodegradability, biocompatibility, non-toxicity and functionality, and have been widely used in the biomedical field (Chen, Xi, and Weng 2022). Therefore, cellulose is a promising material for the preparation of artificial blood vessels and is quite important for either artificial blood vessels or vascular tissue engineering (Choi et al., 2022).

A novel bionic vascular graft scaffold was prepared using

polycaprolactone (PCL), EC, and type I collagen as raw materials using electrospinning method, achieving similar effects to natural small diameter blood vessels (Aydogdu et al., 2019). A layered structure of bacterial cellulose/potato starch composite material was synthesized, and the scaffold had good cell compatibility and blood compatibility (Liu et al., 2022). While improving vascular patency, it can also induce rapid regeneration of blood vessels. In the *in-vitro* evaluation in rabbits, the scaffold material had 75% patency, which has great potential for application as artificial small diameter blood vessel transplantation.

3.3. Application of cellulose in skin tissue engineering

Natural hydrogel produced by cellulose can promote skin tissue regeneration and is widely used as wound dressing. A novel TEMPO-oxidized cellulose nanofiber-silk fibroin scaffold was prepared using a low-cost freeze-drying method (Shefa et al., 2017). The porous structure had a high swelling rate and fast wound healing ability, which can be used as a skin wound healing material in clinical practice. Fontana was the pioneer in the use of BC to replace burned skin (Fontana et al., 1990). However, the lack of 3D microporosity and limited biocompatibility of BC limit its application as a scaffold for skin regeneration *in vitro*. Therefore, it is necessary to introduce controllable three-dimensional microporosity and enhance its biocompatibility through surface modification. BC/gelatin scaffolds were prepared by stomatal induction, surface modification and 3D micropore regeneration (Khan et al., 2018). *In-vitro* biocompatibility test showed that human keratinocytes had good adhesion and proliferation ability. Meanwhile, the skin regeneration rate of experimental animals was as high as 94% within 2 weeks, which is a candidate material for future skin regeneration applications.

3.4. Application of cellulose in bone and cartilage tissue engineering

Tissue engineering has attracted extensive attention in the field of bone tissue regeneration. Suitable mechanical properties are one of the important factors for the application of scaffolds in bone tissue engineering, and their mechanical strength should be well matched with the surrounding healthy bone tissue (Torgbo and Sukyai 2018). Cellulose has unique characteristics such as easy availability, good biocompatibility, and slow degradation. At the same time, its structure is similar to bone 3D extracellular matrix protein (Rajwade et al. 2015). As a composite synthetic bone repair material, it has received widespread attention from bone tissue engineering researchers.

Chondrocytes are the main cells in cartilage. The design and development of cellulose-based scaffolds with simulated ECM biomechanical properties have a significant impact on the successful regeneration of cartilage tissue (Mardones et al. 2015). Several studies have investigated the use of cellulose and its derivatives-based scaffolds, and their application in cartilage in combination with other natural/artificial polymers. A porous composite material made of fibroin protein and cellulose was created as a suitable scaffold for bone tissue engineering (Burger et al., 2020). Compared with the silk fibroin control material, the cellulose composition improved the mechanical properties of the hydrogel. Hydrogel supported MC3T3 cells to differentiate into osteoblasts, which was expected to be a good scaffold material for bone tissue engineering. Chondrocytes cultured in monolayer for 9 days were inoculated into BC scaffolds and grew well (Gea et al., 2018). This preliminary data provides hope for BC gel as a potential alternative scaffold material for cartilage tissue.

3.5. Application of cellulose from tissue engineering to cultivated meat

In summary, cellulose and its derivatives has been widely studied and applied as scaffolds in tissue engineering due to its unique properties, ease of production, and simplicity of the functionalization process. The fiber structure and surface properties of cellulose scaffolds can provide a good substrate for cell attachment and promote cell adhesion and proliferation. The introduction of growth factors, drugs, or other bioactive substances into cellulose scaffolds can be explored to enhance the effectiveness of cell growth, differentiation, and repair. Using co-axial electrospinning technology, aloe vera extract was embedded in polymer fibers containing chitosan, polycaprolactone, and keratin (Zahedi et al., 2019). The presence of aloe vera can promote cell growth and adhesion without any cytotoxic effects. *In-situ* modification was used to add carboxymethyl to BC in order to improve its biocompatibility and medical performance (Zhou et al., 2019). Carboxyl methylation significantly improved cell affinity and viability by partially altering the structure and physical properties of BC.

The fiber structure, porosity and mechanical properties of cellulose scaffolds can also be modulated by different preparation methods and conditions. For example, macroporous BC was obtained by freeze-drying method, and enhanced the biocompatibility of BC by flushing the BC membrane with polyethylene glycol (PEG-400) (Eroglu and Coral 2021). The prepared scaffolds obtained were good candidates for 3D tissue engineering scaffolds in terms of water retention, porosity and cell support capacity.

In conclusion, the above studies of cellulose scaffolds in the field of tissue engineering can provide much inspirations to the field of cultivated meat scaffold aspect. These studies can help to improve the structure and performance of the scaffolds, optimize the cell culture conditions, understand the adaptability of different types of cells to cellulose, and promote the application of cellulose scaffolds in the field of cultivated meat.

4. Potential preparation methods of cellulose-based scaffolds for cultivated meat application

Methods for the preparation of cultivated meat biomaterials have been reviewed in the literature (Bomkamp et al., 2022; Ng and Kurisawa 2021; Seah et al., 2022). Among them, the methods used for the preparation of porous scaffolds include particle leaching, melt forming, freeze-drying, foaming, etc.; the methods used for the preparation of fibrous scaffolds include wet spinning, electrostatic spinning, rotary jet spinning, etc.; the methods used for the preparation of hydrogels include enzymatic gelation, thermal gelation, photopolymerization and ionic crosslinking gelation, etc.; the methods used for the preparation of spherical structures include emulsification, microfluidization, etc.; 3D printing, plant decellularization, extrusion, etc. can also be used for the preparation of cultivated meat biomaterials. Among the above mentioned preparation methods, those applicable to cellulose (which may require other edible materials) are freeze-drying, foaming, enzymatic gelation, thermal gelation, photopolymerization and ionic crosslinking gelation, 3D printing, and plant decellularization, while other methods are not suitable due to the potential introduction of large amounts of inedible solvents. Previous literature has focused on biomaterial types, while biomaterial structures directly affect the application scenarios of biomaterials in cultivated meat. Therefore, this review presents cellulose-based biomaterial preparation methods for cultivated meat in order of key biomaterial structures: porous, spherical, oriented, natural precise, and customizable structure (shown in Fig. 2 and Table 1).

4.1. Methods for porous structure

In order to satisfy 3D cell culture, the biomaterials should have a properly-sized, interconnected porous structure. If the pores are too small, the cells will not be able to migrate to the inside of the scaffold. However, if the pores are too large, cell productivity is reduced (O'Brien et al., 2004). Therefore, preparation methods that can create pores close to, but slightly larger than, cell size are widely used in this field. Common methods include freeze-drying, foaming, sacrificial material, and directional freezing.

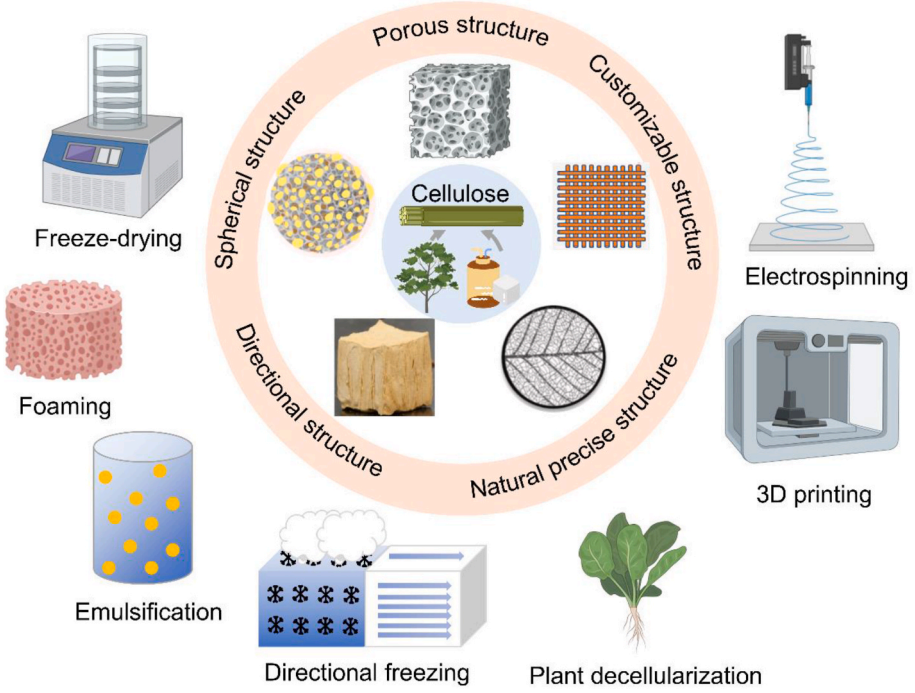

Fig. 2. Potential preparation methods of cellulose-based biomaterials for cultivated meat application.

4.1.1. *Freeze-drying*

Freeze-drying is a commonly utilized method of porogenesis that is primarily employed for the preparation of porous scaffolds. Initially, the water molecules in the material are frozen at temperatures below the freezing point of water, which leads to the displacement of surrounding molecular chains. Subsequently, under a high vacuum, the ice sublimates directly into vapor, resulting in the preservation of the pores formed by the ice grains. It should be noted that the homogeneity of the pore sizes throughout the substrate is dependent on the cooling rate. Slower cooling rates tend to create homogeneous, equiaxed grains, which are advantageous for cell growth without the need for directional alignment (O'Brien et al., 2004).

Acetylated CNC porous scaffolds with inner pore sizes of 0.1–10 μm were prepared by freeze-drying using water as a solvent (Abraham et al., 2017). The cellulose formed interconnected lamellar layers with thicknesses of 40–80 nm under spatial extrusion of the ice template. Unfortunately, the study did not verify the biocompatibility. Cellulose microfiber-gelatin porous scaffolds were prepared by freeze-drying at −20 °C (Xing et al., 2010). The obtained scaffolds had the internal pore size of approximately 70 μm, the porosity of approximately 70%, and the Young's modulus of 1–3 MPa (corresponding to 50–75% cellulose content in the samples). After 28 days of culture, human mesenchymal stem cells (hMSCs) proliferated actively in the scaffold, expressing a large amount of F-actin and extracellular molecule networks, and presenting a tendency to align along the cellulose fibers. Subsequent induction culture revealed that the scaffolds allowed hMSCs to differentiate successfully into osteoblasts or adipocytes. However, gelatin is of animal origin, and inedible 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS) were added to crosslink the gelatin in the study.

The freeze-drying method is simple and easy to use; however, it has high energy consumption and cost. If applied to the preparation of cultivated meat biomaterials, it will add an additional burden to the cost of the cultivated meat products. Additionally, the efficiency of freeze-drying is low for large-volume samples, and it is difficult to ensure the uniformity of pores within the biomaterial.

4.1.2. *Foaming*

Foaming is a method of creating pores in a material by producing foams through physical (e.g., gas sparging), chemical (e.g., baking powder), or even biological (e.g., yeast) means (Drenckhan and Saint-Jalmes 2015) and stabilizing the foams before fixing the porous structure of the material. Available foaming agents include physical foaming agents, chemical foaming agents, and surfactants. The main advantage of foaming is the ability to create a clear porous structure. However, its disadvantages include (1) a wide range of pore sizes, which are not easy to regulate; (2) easy to produce closed pores with limited pore connectivity; and (3) uneven pore distribution.

Physical foaming agents are represented by supercritical CO_2. Poly (butylene succinate)-CNC scaffolds with a bimodal open-pore structure were prepared using supercritical CO_2 by two-step depressurization (Ju et al., 2020). The scaffolds containing 5% CNC had pores with diameters of approximately 68.9 μm and approximately 11.0 μm, with a high open porosity (approximately 95.2%). Although poly (butylene succinate) used in this study is not edible, the physical foaming method itself does not affect the edibility of the scaffolds, and is cost and energy efficient, allowing for industrial production. For chemical foaming agents, the decomposition temperature should be lower than that of cellulose and its edible derivatives such as CMC, microcrystalline cellulose (MCC), MC, HPMC, with an initial decomposition temperature (T_d) (of about 230–360 °C (Huang and Li 1998; Li et al. 1999; Nada and Hassan 2000)) to ensure the integrity of the structure and mechanical properties of cellulose biomaterials. In addition, considering the edibility of cultivated meat biomaterials, the introduced foaming agent should not contain toxic, hazardous substances or unpleasant tastes and odors, and should be allowed to be added to food, so only a few foaming agents such as sodium bicarbonate are available. Meanwhile, attention should be paid to the selection of foaming agent, dosage, and foaming process when attempting to obtain open porous biomaterials.

4.1.3. *Sacrificial material*

Sacrificial material is a method of adding macro-, micro- or even nanoparticles as placeholders during the preparation of cellulose biomaterials to create pores. After the cellulose biomaterial is formed, the sacrificial material is then removed, leaving pores close to the size of the

Table 1
Summary of potential preparation methods of cellulose-based biomaterials for cultivated meat application.

Structure	Method	Scaffolding materials	Auxiliaries	Cells	Structural characteristics
Porous structure	Freeze-drying	Highly acetate esterified CNC	Catalyzer: iodine	N/A	Interconnected highly porous scaffolds with continuous, interconnected strong network of ultrathin modified cellulosic layers; 0.1–10 μm pore diameter, 40–80 nm cell wall thickness (Abraham et al., 2017)
		cellulose microfibers and cross-linked gelatin	Crosslinkers: 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS)	Brain cells and human mesenchymal stem cells (hMSCs)	Porous, interconnected, rough 3D scaffolds; approximately 70 μm pore diameter (Xing et al., 2010)
	Foaming	Poly (butylene succinate) (PBS) and CNC	Porogen: supercritical CO_2	NIH-3T3 mouse fibroblast cell lines (NIH-3T3s)	Well-defined controllable bimodal open-pore interconnected scaffolds; approximately 68.9 μm large pore and approximately 11.0 μm small pore diameter (Ju et al., 2020)
	Sacrificial material	BC	Porogens: paraffin wax and potato starch, surfactant: Berol 543, starch degrading enzyme: Termamyl Ultra 300L	Smooth muscle cells (SMCs)	3D nanofibril-network tubular scaffolds with controlled microporosity; 5–100 μm potato starch particle diameter, 90–500 μm paraffin particle diameter (Bäckdahl et al., 2008)
		BC	Agarose	Human P1 chondrocytes	3D scaffolds containing a continuous, interconnected network of pores with diameters ranging from 300 to 500 μm (Yin et al., 2015)
	Salting-out	Chitosan-poly(vinyl alcohol)-CMC	NaCl	L929 fibroblast cell lines	Biomimetic scaffolds with a uniformly distributed and interconnected pore structure; 13.6–15.5 μm pore diameter (Kanimozhi et al., 2018)
Spherical structure	Emulsification	Crosslinked poly (vinyl alcohol) and CNF	Crosslinker: glutaraldehyde, oil phase: Span 80 and toluene, cleaner: hexanes	NIH-3T3s	Highly porous aerogel micro-spheres with two particle sizes; approximately 94.5 μm and approximately 503.9 μm particle diameters; approximately 2.1 μm and approximately 24.9 μm pore sizes (Zhang et al. 2017)
	Emulsification/ microfluidics/ sacrificial material	BC	Gelatin, corn oil, Span 80, sodium alginate, $CaCl_2$, ethylenediamine tetraacetic acid (EDTA) or sodium bicarbonate	N/A	Nanofibrous microspheres with minimum size of 10 μm (Higashi and Miki 2015, 2018)
Directional structure	Directional freezing	Hydroxyapatite and chitosan	Heat control: heater and liquid nitrogen, crosslinker: glutaraldehyde	N/A	Hierarchical porous scaffolds with tunable unidirectional channel structures; 10–100 μm and 1–50 μm channel sizes (Liaw et al., 2020)
		Noncrosslinked collagen	Collagen fibrillogenesis: ammonia, cooling source: liquid nitrogen,	Normal human dermal fibroblasts (NHDFs) and mouse C2C12 myoblast cell lines (C2C12s)	Highly porous and anisotropic fibrillar scaffolds with pores patterned with regularly spaced microridges; 12–15 mm length and 5–6 mm diameter; 25–95 μm (bottom) and 50–270 μm (top) pore sizes, 6.9–10.0 μm (bottom) and 14.5–18.9 μm (top) distances between ridges (Rieu et al., 2019)
		Silk fibroin- poly (ethylene glycol) (PEG)-CNC	Silk fibroin dissolving: Na_2CO_3 and LiBr, cooling source: liquid nitrogen	N/A	Anisotropic cryogels with an orientated microstructure; 11–17 μm average pore sizes (Dai et al., 2021)
		Cationic CNF	Cellulose modifier: glycidyl trimethylammonium chloride (GTMAC), crosslinker: glyoxal, oil phase: cyclohexane, cooling source: liquid nitrogen	MG-63 human osteosarcoma cells	3D foam scaffolds with internal architecture of aligned smooth walled micro channels; approximately 35 μm average channel size and approximately 26 nm wall diameter (Courtenay et al., 2019)
Natural precise structure	Plant decellularization	Apple hypanthium tissue	Decellularization: sodium dodecyl sulfate (SDS), functionalization: collagen, crosslinker: glutaraldehyde	NIH-3T3s, C2C12s, human HeLa epithelial cells	3D highly porous scaffolds (Modulevsky et al., 2014)
		Spinach leaves	Cuticle removal: hexanes; decellularization: SDS, Triton X-100, bleach	Primary bovine satellite cells	Scaffolds with vascular networks (Jones et al. 2021)
		Celery stalks	Decellularization: sodium dodecyl sulfate (SDS)	C2C12s	Scaffolds with 10–100 μm wide parallel microchannels (Campuzano et al. 2020)
		Amenity grass	Decellularization: SDS, Tween-20, bleach	C2C12s	Scaffolds retaining natural striated topography; approximately 75 μm blade thickness; channels less than 1 μm, 1–5 μm, and up to approximately 100 μm (Allan et al. 2021)
		Jackfruit	Decellularization: SDS, colour control: sodium bicarbonate	Primary porcine myoblasts	Scaffolds having the natural structures to recapitulate marbling visuals of meat

(*continued on next page*)

Table 1 (*continued*)

Structure	Method	Scaffolding materials	Auxiliaries	Cells	Structural characteristics
					cuts and exhibitng a meat-like browning behaviour when cooked (Ong et al., 2021)
Customizable structure	3D printing	Gelatin-cellulose-alginate	Crosslinker: glutaraldehyde or $CaCl_2$	NIH-3T3s	Hydrogel-based 3D printer ink (Erkoc et al., 2020)
		CNF-CMC	N/A	Human bone tissue derived osteoblast cells (hFOB)	Fibrous inks and dual porous scaffolds; 200–500 μm macropore diameter, 20–90 μm micropore diameter (Mohan et al., 2020)

microspheres. Both the sacrificial material method and the foaming method mentioned above can be classified as the use of porogens, but they differ in their principles. Foaming involves the physical, chemical, or biological generation of gases by porogens to create pores, while the sacrificial material method involves the physical occupation of space by the solid porogens themselves, which is subsequently removed to create pores.

Paraffin wax particles (90–500 μm in diameter) and potato starch particles (5–100 μm in diameter) were used as sacrificial materials, added into *K. xylinus* fermentation system, and removed after the BC generated, to obtain microporous scaffolds for culturing SMCs (Bäckdahl et al., 2008). However, the use of surfactants and enzymes in the purification of the scaffold will adversely affect its edibility and cost. Agarose microspheres were used as sacrificial materials to embed into the strains membrane growing layer by layer to obtain porous BC scaffolds (Yin et al., 2015).

4.1.4. Salting-out

The salting-out method, which uses salt crystals (commonly sodium chloride) as a sacrificial material to create a porous structure, has a lower cost and is easier to purify (NaCl can be leached with water) without introducing toxic and hazardous chemicals than the sacrificial material method mentioned above. Chitosan, poly(vinyl alcohol) (PVA) and CMC were mixed with water, added with NaCl particles (200–500 μm in diameter), and then air-dried (Kanimozhi et al., 2018). NaCl was removed with water and air-dried again to obtain porous scaffolds with pores of 13.6–15.5 μm in diameter. The pore size, porosity, and pore openness of the scaffolds were higher than those of the freeze-drying control group.

4.2. Methods for spherical structure

The commonly used methods of preparing cellulose microspheres, including emulsification and microfluidization, have been fully reviewed by predecessors (Carvalho et al., 2021). PVA/CNF porous microspheres were prepared by emulsification with water in oil combined with freeze-drying (Zhang et al. 2017). NIH-3T3s grew well on the surface of the microspheres after 10 days of culture, and some cells were able to migrate into the pores inside the microspheres. The main advantage of the microcarrier is that the emulsification process is conducive to large-scale production.

For the preparation of cellulose-based spheres used in cultivated meat, the main problem of the above methods is the consumption of large amounts of solvents, most of which are inedible or cumbersome to remove. Residues may not only harm human safety, but also negatively affect the surface properties of materials such as wettability, roughness, surface charge, and exposure degree of functional groups, hindering the adhesion and growth of cells on the biomaterials. To address this problem, the above methods can be combined with the *in-situ* cellulose production by microbial fermentation, thus avoiding the introduction of solvents. For example, gelatin microspheres containing BC-producing bacteria are first produced by microfluidics or emulsification, and then used to construct hollow microsphere spaces for bacterial growth, thus forming cellulose microspheres (Higashi and Miki 2015, 2018). In the process of avoiding the use of toxic and difficult-to-remove solvents, the cellulose microspheres prepared in a few studies are edible in terms of raw materials and methods, but the particle diameters tend to be large. Another example, cellulose microspheres prepared by the dropping method using NaOH aqueous solution as the solvent have an average diameter of about 0.5–4 mm (Gericke et al. 2013; Rosenberg et al., 2008; Sakurai et al., 1997; Sescousse et al. 2011). In addition, the above methods need to be combined with other methods to immobilize the microsphere morphology. For natural cellulose that is relatively insensitive to acid, alkali, temperature, and pH, the auxiliary method is mostly freeze-drying.

4.3. Methods for directional structure

Anisotropic biomaterials can be formed by directional freezing, mechanical stretching, etc.

4.3.1. Directional freezing

Directional freezing, also known as freeze-casting, is a method used to create channels in biomaterials running parallel to the direction of the temperature gradient. This is accomplished by freezing water or salt solutions in the substrate with a gradient temperature field, forming ice pillars, and then removing them after freeze-drying. The diameter of the created channels is mainly determined by the freezing temperature.

Chitosan was combined with hydroxyapatite and directionally frozen to create internal channels with diameters of 10–100 μm and 1–50 μm at cooling rates of 2 °C/min and 5 °C/min, respectively (Liaw et al., 2020). The collagen solution was directionally frozen at a cooling rate of 5 °C/min to obtain a scaffold channel of 25–270 μm (Rieu et al., 2019). Anisotropic silk fibroin-CNC scaffold was prepared by directional freezing with liquid nitrogen (Dai et al., 2021). As the CNC concentration increased to 0.8%, the average aperture of the scaffold increased to 17 μm. Considering that silk fibroin is also edible (Marelli et al., 2016), the silk fibroin-CNC composite is acceptable in cultivated meat biomaterials. Cationized CNF scaffolds with aligned smooth microchannels were obtained by directional freezing with liquid nitrogen as the cooling source (Courtenay et al., 2019), the channel diameter was approximately 35 μm.

Directional freezing is a simple and efficient method of creating directional channels in biomaterials using ice as a sacrificial template. However, as the size of the sample increases, especially in its length along the direction of the temperature gradient, it becomes harder to ensure a consistent temperature gradient throughout the sample, leading to channels of uneven diameters (the local temperature gradient near the cold source is greater, thus producing smaller channels (Deville et al. 2007), therefore preventing the achievement of both good channel length and channel aperture uniformity. This problem hinders the potential of directional freezing for mass production of directional scaffolds, especially large ones for whole-cut meat.

4.3.2. Mechanical stretching

Mechanical stretching is a method that applies tension to the

material in one direction, resulting in higher orientation in the stretching direction. Its directional effect is affected by mechanical properties (such as elastoplasticity), natural structure, tensile mode, and other factors. The main advantage of this method is its simplicity, cost-effectiveness, efficiency, and scalability. The BC pellicle was wet stretched at 40% strain and then hot pressed at 60 °C to fix the structure to obtain a highly oriented aligned fiber structure (Wang et al., 2018). Four forms of 3D materials with anisotropic structure and mechanical properties were obtained by parallel lamination, orthogonal lamination, axial rolling, and concentric rolling of multiple layers of stretched materials based on linear mechanical stretching of single-layer materials (Mredha et al., 2019). This can be used to prepare anisotropic cellulose-based cultivated meat scaffolds to produce tunable, whole-cut meat with multiple textural orientations and multiple levels of chewiness.

4.3.3. Orientation specific to BC

In addition to the above methods, highly oriented structures can be created for BC in the following specific ways: during the fermentation of BC-producing microorganisms, the movement paths of microorganisms can be restricted to linear channels by introducing striated groove templates (Prathapan et al., 2020) (i.e., template method), microorganisms can be induced to move along the direction of electric field forces by applying electrostatic fields (Sano et al., 2010) (i.e., electric field method), and by using cylindrical stirred bioreactors with oxygen-permeable outer walls (Luo et al., 2018) (i.e., rotary agitation method), all of which allow *in-situ* generation of oriented BC scaffolds. By placing the molds with needle arrays into the microbial culture system for static fermentation (Rambo et al., 2008) (i.e., mold method), BC with internal oriented channels can be obtained.

4.4. Methods for natural precise structure

Decellularization, a method of obtaining ECM and skeletal structure by removing cell contents from tissues or organs, has received sustained attention within the field of tissue engineering and regenerative medicine in recent years. By directly acquiring ECM rather than simulating it, this approach can achieve biocompatibility unmatched by other biomaterials, and its raw materials are often widely available. Currently, decellularization is mainly studied in plants and animals rather than microorganisms. In consideration of animal welfare, production cost, and difficulty of decellularization operation, plants are preferred as raw materials for decellularization biomaterials used in cultivated meat.

The roots, stems, and leaves of plants, as vegetative organs, have natural channels that can transport water and nutrients with a wide range of diameters, which can meet the various needs of pores of biomaterials. The original parenchyma cells and other cells are neatly arranged. These natural structures can be maintained by residual cell walls after the removal of cell contents, which is conducive to being used as biomaterials to assist in whole-cut cultivated meat production. The main chemical composition in the cell wall is natural cellulose, which has hydrophilicity, durability, biocompatibility, and edibility.

The roots, stems, leaves, and fruits of plants have been studied for the preparation of decellularized biomaterials. Among them, stems, leaves, and fruits of vegetables and fruits are more common used in existing studies. Decellularization preserves the structure of specific tissues such as vessels and vascular bundles, which facilitates the attachment, alignment, migration, differentiation, and nutrient exchange of the inoculated cells. Therefore, this method has become a hot topic in biomedical engineering (such as alternative organs (Zhu et al., 2021)), and has been used in cultivated meat biomaterials. For example, Amenity grass was decellularized and the cell growth effect was tested with C2C12s (Allan et al. 2021). It was found that the natural grooves of grass give it a superior ability to induce cell orientation. Decellularized spinach leaves with vascular networks were used to culture primary bovine satellite cells (Jones et al. 2021). The cells on this scaffold can maintain high cell activity (99%) for a long time (14 days). For details of plant species and parts, methods, and reagents commonly used in plant decellularization, please refer to the existing review (Zhu et al., 2021); this will not be repeated here.

The advantages of plant decellularization for cultivated meat biomaterials are as follows.

(1) Decellularization can make full use of the natural 3D porous structure left by plants after the removal of original cells, effectively simplifying the biomaterial preparation process and providing an appropriate growth space and real extracellular environment for target cells. Further, decellularization helps to obtain delicate and sophisticated microscopic scaffolding structures that are difficult to obtain by conventional means, such as vessels, vascular bundles and other directional structures can induce cell alignment (Cheng et al., 2020; Fontana et al., 2017; James et al., 2020) and nutrient transport, facilitating the formation of whole cultivated meat tissue.
(2) If the stems, leaves, and fruits of common vegetables and fruits are used for cellularization, the raw materials are widely sourced, green, natural, renewable, relatively low cost, and edible, and the high-value utilization of some agricultural and forestry wastes can be realized.
(3) Some decellularization reagents (e.g., ethanol, acetic acid, sodium chloride, sodium hypochlorite) and decellularization methods (e.g., chemical immersion (Fontana et al., 2017)) are low-cost and readily available or achievable, which facilitates large-scale production.
(4) Some decellularized plant biomaterials can achieve high cellular activity of approximately 95% or more (Allan et al. 2021).

Despite the advantages of decellularized cultivated meat biomaterials, there are some drawbacks to consider.

(1) The current mainstream decellularization method, i.e., using detergent, requires a long processing time, which is not conducive to commercialization. For instance, spinach leaves treated with sodium dodecyl sulfate (SDS) require more than 10 days from pretreatment to freeze-drying (Jones et al. 2021).
(2) The edibility of the decellularized biomaterial is questionable. Although edible fruits and vegetables (such as apple, spinach, celery, scallion, etc.) are preferred as raw materials in the present studies, the use of chemical reagents to remove cells may lead to the risk of inedible substances residues (such as the surfactant SDS), and their residues should be disclosed by more studies and compared with relevant food standards. Some researchers have mentioned safe alternatives to toxic and hazardous agents (such as replacing Triton X-100 with polysorbate 60 (Jones et al. 2021)), but the decellularization effect of related alternatives needs to be further confirmed. At the same time, some chemical treatments may introduce odors (e.g. sodium hypochlorite, acetic acid) into the biomaterial and then into the cultivated meat product. In addition, nutritional evaluation and sensory evaluation of biomaterials need to be further studied.
(3) Variability will inevitably exist among different individuals of the same type of raw material, and even among different parts of the same individual, resulting in discrepancies between different batches of biomaterials, which is not conducive to commodity standardization.
(4) The success of the decellularized plant biomaterials with good cellular activity is mainly attributed to the good pore structure or directional micropattern. The performance of the decellularized plant biomaterials without these structural advantages is not satisfactory (Lee et al., 2019). Although the poor performance may still be blamed on several non-structural physical properties (such as surface wettability and elastic modulus), it seems to

confirm the deficiency of natural cellulose, the main chemical component of cellulose-based biomaterials, in cell adhesion.

4.5. Methods for customizable structure

3D printing, also known as additive manufacturing and rapid prototyping, is a material preparation method that builds rheological materials into 3D objects with precise structure by stacking them layer by layer through computer-aided design and digital manufacturing (Aguiar 2018). 3D printing can be divided into seven categories (Li and Pumera 2021), of which the four more accepted in the food field are (1) selective laser sintering, (2) hot air sintering, (3) liquid binding, and (4) extrusion method (Mantihal et al. 2020). 3D printing can reduce raw material loss, and by using the same set of equipment, products with a variety of complex structures can be manufactured. The "freedom to customize" feature is particularly important in the early development stages of biomaterials used in cultivated meat, as it allows researchers to extensively try and select suitable structures of biomaterials. In biomedical engineering, the applications of 3D printing continue to expand, ranging from drug delivery systems and microvessels to artificial organs and even patient anatomical models (to aid surgery) (Atala, 2020; Lai et al., 2021).

Bioink with a gelatin-cellulose-alginate composite was formulated to take into account the rheology and cytocompatibility of bioink, and mechanical properties of extruded material (Erkoc et al., 2020). Through extrusion 3D printing, four structures of hydrogels were obtained, including multilayered 3D-filled and hollow cylindrical structures, conical structures, lattice structures with cylindrical and square holes, and anatomical mimic artificial ears.

Only cellulose and its derivatives (CMC and CNF) as raw materials and water as a solvent were used to prepare inks and fabricate physical crosslinked scaffolds with an adjustable macropore (200–500 μm) mesh structure by 3D printing, freeze drying, and dehydrothermal treatment (Mohan et al., 2020).

5. Challenges and innovations

5.1. Cell adhesion

Natural cellulose has a hydrophilic surface with low non-specific protein adsorption (i.e., there is no cell anchor such as RGD), which is not conducive to mammalian cell adhesion (Courtenay et al., 2017). This is the biggest challenge for cellulose as raw material of cultivated meat biomaterials.

The introduction of the RGD tripeptide (Arginine-Glycine-Aspartate, Arg-Gly-Asp) can enhance the cell adhesion of cellulose. RGD is a bioactive cell adhesion sequence found in ECM that can bind specifically to integrin (which mediating recognition and adhesion of cells to the ECM or to other cells) on the cell surface. Therefore, RGD peptides or RGD-containing proteins, such as fibronectin, laminin, vitronectin, collagen, or gelatin, can be modified on cellulose surfaces. However, RGD has limited adsorption to non-protein substances such as cellulose, so cellulose-binding modules (CBMs, which have both high affinity and specificity for cellulose surfaces and the ability to bind virtually any bioactive protein) can be introduced as a bridge to achieve the firm cellulose-RGD connection (Andrade et al., 2010).

Surface charge modification can enhance cell adhesion of cellulose. One way is functional group modification, including cationization such as the introduction of quaternary ammonium groups, and strong anionization such as the introduction of -SO_3. Functional group modifications to regulate the surface charge of cellulose have been used in commercial biomaterials. For example, the main components of Cytopore™ microcarrier are positively charged diethylaminoethyl (DEAE) cellulose, while that of GrowDex-T hydrogel is negatively charged cellulose, both of which enhance cell adhesion. When using this method, attention should be paid to whether the modified functional groups will damage the edibility of cellulose. For example, although quaternary ammonium salt is a representative substance to give cations and thus improve the cell adhesion of cellulose, it is usually not edible, and the corresponding modified cellulose is not within the range of approved food additives. Cellulose modified with carboxymethyl groups is edible and can improve cell adhesion (Golizadeh et al., 2019). In addition to functional group modification, another approach is to combine cellulose with other cationic substances to change the surface charge, such as natural cationic polysaccharides: chitin/chitosan. This recombination can be physical blending or chemical crosslinking, and can be carried out in one of several steps, such as cellulose preparation (e.g., adding in BC fermentation system), cellulose pretreatment (e.g., blending with pretreated cellulose), and biomaterial preparation (e.g., soaking biomaterials into modifiers).

5.2. Cost and scaling up

For the cultivated meat industry, fields including tissue engineering have provided a solid technical foundation, so the more pressing issue is how to reduce costs and expand the scale. Cellulose, as a potential raw material for cultivated meat biomaterials, also needs to be taken into consideration. The cost of cellulose can be roughly divided into production costs in the early stage and purification costs in the late stage.

For plant cellulose, its resources are rich, extensive, and easy to obtain. The main sources of commercial plant cellulose are wood and cotton, so the upfront production cost is low. The content of cellulose in cotton is up to 90%, but the proportion of cellulose in wood is about 40–47%. The cell wall, where cellulose is located, also contains hemicellulose, lignin, pectin, and other components. Therefore, a series of extraction and purification operations are needed to achieve the high purity and uniform specific fiber morphology of the raw materials required for edible biomaterials. At present, plant cellulose has developed mature and inexpensive purification processes (mainly acid hydrolysis and mechanical treatment, as described in the previous section of "Plant cellulose"). Relevant studies (Posada et al., 2020; Reiner and Rudie 2017) showed that plant nanocellulose (CNF, CNC) has achieved mass production worldwide and the yield is still expanding, from 20 kg/day in the Netherlands to 2000 kg/day in the United States, and it is planned to reach 33 million t/year. However, in order to avoid irreversible agglomeration or hornification of nanocellulose, it needs to be preserved in an aqueous solution, which increases the transportation cost on the one hand, and increases the loss cost due to microbial breeding on the other hand. In this regard, the cellulose can be dried first, and then dispersed after arrival. Among oven drying, freeze drying, spray drying, and supercritical drying, freeze drying and supercritical drying can avoid agglomeration and achieve redispersal, but the cost of freeze drying is more acceptable.

For BC, the purity of cellulose is much higher than that of plant cellulose, which greatly reduces the complexity of the purification process. However, the upstream BC production process (i.e., the traditional static microbial fermentation process) has many problems, such as discontinuous production status, long production time for a single batch, large space, large labor force, and low yield, resulting in a high comprehensive cost of BC (Shi et al., 2014; Wang et al., 2019) (80 times that of plant cellulose (Sharif et al., 2020)). In this regard, we can start from strain, culture medium, culture conditions, and bioreactor.

(1) Bacterial strains. Natural mutant screening can be carried out to obtain high BC production strains. At the same time, genetic modification to produce high-yielding strains may be acceptable because the transgenic ingredients are theoretically absent from BC and BC undergoes an intense purification process (e.g., boiling in approximately 1M NaOH for 1 h) that removes the bacteria carrying the transgenes.
(2) Culture media. Synthetic media is one of the main factors causing a high production cost of BC (Gorgieva and Trcek 2019). Waste

products can be developed as medium components (primarily carbon sources), such as glycerol remaining from biodiesel production and grape bagasse (Vazquez et al., 2013), rotten banana unsuitable for human consumption (Molina-Ramirez et al., 2020), thin stillage (Revin et al., 2018; Wu and Liu 2013), cheese whey (Revin et al., 2018), beet molasses (Keshk et al. 2006) and so on. Compared with the synthetic, typical HS (Hestrin and Schramm) medium, these media can reduce the cost and even increase the yield.

(3) Culture conditions. Culture conditions with lower energy consumption can be found, for example, by carrying out domestication of the strain to make it resistant to the low temperature of 10–20 °C (the appropriate temperature for the general strain is about 25–30 °C), so as to meet the needs of BC culture in cold areas (Zhong 2020).

(4) Bioreactors. Bioreactors for BC can provide high efficiency, scale, and continuous production conditions, so we can design and optimize the bioreactors, including reactors for the fermentation process in "relatively static conditions", such as in rotary discs reactor, rotary biofilm contactor, aerosol bioreactor, membrane bioreactor, and horizontal lift reactor, as well as reactors for the fermentation process in agitated conditions, like spherical type bubble column bioreactor, air-lift reactor, and modified air-lift reactor (Shi et al., 2014).

5.3. Processibility

The non-fusible and insoluble characteristics of natural cellulose make it a challenge to process. Specifically, on the one hand, natural cellulose does not melt and breaks down directly at high temperatures. On the other hand, natural cellulose has low solubility, being insoluble in common aqueous and organic solvents, but soluble in lithium chloride/N,N-dimethylacetamide (LiCl/DMAc), N-methylmorpholine-N-oxide (NMMO), NaOH/urea aqueous solution and other solvent systems. However, these known solvents are not edible or even toxic and hazardous, making it difficult to apply them to cultivated meat biomaterials. There are two mainstream views on the mechanism of cellulose dissolution. One is that solvents break intra- and intermolecular hydrogen bond networks. In contrast, another view holds that cellulose has amphiphilic properties, and solvents eliminate hydrophobic interactions between cellulose molecules, which strongly influence dissolution (Medronho and Lindman 2015).

To address the difficulty of natural cellulose processing, chemical modification of cellulose can enhance water solubility. Decreasing DP or molecular weight also contributes to cellulose dissolution. In addition, it is possible to choose processing methods that applies to cellulose dispersions (rather than solutions only) to avoid the introduction of inedible solvents.

5.4. Mechanical properties

Stiffness is one of the most important mechanical properties of biomaterials. Both muscle and adipose cells are sensitive to substrate stiffness, but different cell types have different requirements for stiffness. Taking muscle cells as an example, although myotubes can form on substrates of varying stiffness (Callue 2020), the length of myotubes and the number of myotube clusters are different (Palchesko et al., 2012), and myotubes containing myosin/actin striations appear only at approximately the stiffness of natural skeletal muscle (approximately 12 kPa) (Engler et al., 2004). Based on the cell-stiffness response, it has been summarized (Bomkamp et al., 2022) that for myogenic cells and for adipogenic cells culture, respectively, the ideal Young's moduli of biomaterials are 12–21 kPa and 2–3 kPa. In addition to cell proliferation and differentiation, from the perspective of food taste, cultivated meat biomaterials should have moderate stiffness after cooking to ensure good chewability and realistic imitation of meat, although research on the mechanical properties of heat-treated biomaterials is very limited at present.

Cellulose itself is stiff; for plant cellulose, the Young's modulus of MCC is approximately 25 GPa (Eichhorn and Young 2001). Affected by anisotropy, defects in nanocrystals, crystallinity, size, measurement methods, and other factors, the value of Young's modulus of CNC can range from 7.5 to 143 GPa (George and Sabapathi 2015). The Young's modulus of a single BC fiber is approximately 80 GPa (Guhados et al. 2005), and the Young's moduli of BC pellicles were measured to be 200–500 MPa and 1–10 MPa, respectively, via biaxial and uniaxial tensile tests (Lopez-Sanchez et al., 2014). Although the stiffness of cellulose material itself is large, the stiffness of the finished cellulose-based biomaterial is affected by many factors, such as the properties of the raw cellulose and preparation method, and presents a wide variable range. In general, the stiffness of the biomaterial is determined by material stiffness and structural stiffness from different dimensions. Therefore, researchers can adjust the overall stiffness of the cellulose-based biomaterials from these two aspects.

The ways to adjust the material stiffness of cellulose include compounding with other materials, physical or chemical crosslinking, etc. For example, using alginate (1% w/v) and CNF (0.15–0.75% w/v) as raw materials, $CaCO_3$ and D-glucono-δ-lactone as crosslinking agents, hydrogels with Young's modulus of about 5–60 kPa were prepared (Aarstad et al., 2017). This stiffness range is suitable for the growth of myogenic cells and all of the above materials are edible. For example, collagen functionalization (2.2 ± 0.2 kPa) and glutaraldehyde chemical crosslinking (4.1 ± 0.3 kPa) both increased the stiffness of the decellularized apple tissue (1.1 ± 0.1 kPa) (Modulevsky et al., 2014). However, animal collagen and toxic glutaraldehyde are not suitable for creating cultivated meat biomaterials, so the selection of composite regents and crosslinking regents should be carefully considered. Citric acid is the commonly used cellulose-cellulose crosslinking regent without affecting the edible properties (Singh et al., 2019). For cellulose-composite crosslinking, the use of crosslinking agent and its type depends on the physical and chemical characteristics of cellulose and the composite regent. For example, the Maillard reaction, which occurs when protein and carbohydrate are mixed at high temperatures, can be used to crosslink cellulose with non-animal proteins such as soy protein (Su et al., 2010). In addition, the crystallinity of cellulose is positively correlated with the material stiffness, so cellulose with appropriate crystallinity can be used to prepare biomaterials (Siro and Plackett 2010).

The ways to reduce structural stiffness include making pores and creating directional channels, as mentioned above. As porosity increases, the proportion of substrate providing mechanical support in the biomaterial diminishes, making the structure of the biomaterial looser and reducing its stiffness. Cellulose hydrogels with Young's modulus ranging from 30 kPa to 1.3 MPa can be prepared by adjusting cellulose concentration (Isobe et al., 2018). The Young's modulus of the hydrogel was reduced to 5.4 kPa after the introduction of 300 μm diameter pores by salt leaching.

In addition, to meet the desired biomaterial stiffness, decellularized plant biomaterials seem to be the easiest option. The Young's modulus of plants generally decreases after decellularization, and the Young's modulus of most unmodified decellularized plants is in the range of approximately 1 kPa (apple hypanthium) to 21 kPa (spinach leaf) (Harris et al. 2021), which is close to the expected stiffness of cultivated meat biomaterials and can save a lot of additional manipulation. Of course, this appropriate modulus range is also facilitated by the researchers' preference for softer plant samples, such as grass leaves. In fact, the stiffness of decellularized plants can fluctuate in a wide range of Young's modulus from kPa to GPa, under the influence of various factors such as species and parts of plants, and processing methods.

6. Conclusions

In this review, we explored the potential and challenges of using cellulose in cultivated meat biomaterials. The cultivated meat industry is in need of affordable, non-animal, and edible raw materials. Cellulose, particularly when sourced from non-animal origins, offers a significant cost advantage. Furthermore, the existing research and commercial infrastructure in the medical and biological fields positions cellulose as a high-quality biomaterial source, with the potential to drive the growth of the cultivated meat industry. We presented various methods for preparing cultivated meat biomaterials with cellulose. These methods allow the creation of diverse structures, such as porous, directional, and microsphere configurations, depending on the requirements. To address challenges related to cellulose, we discussed strategies like enhancing cell adhesion, improving solubility through cellulose derivatives, and adjusting stiffness through various means. Notably, the use of decellularized plants presents a direct and practical solution to some of these challenges. In conclusion, while the processing of plant cellulose is well-established, bacterial cellulose (BC) and decellularized plants show promise in the field of cultivated meat biomaterials due to their adaptability in forming and the ease of achieving precise structures. The design and optimization of cellulose-based biomaterials are areas ripe for further exploration and research by relevant professionals, which will undoubtedly expedite the integration of cultivated meat into our daily meals.

Author contributions

Yunan Tang and Chenchen Shi are responsible for software, investigation, visualization, writing-original drafts. Yuyan Zhu, Qiong Wang, Ming Yang is responsible for data curation and writing-original draft. is responsible for data curation and writing-original draft. Kuichuan Sheng is responsible for supervision, writing-review & editing. Ning Xiang and Ximing Zhang are responsible for conceptualization, funding, acquisition, resources, supervision, writing-review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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