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Natural Scaffolds Used for Liver Regeneration: A Narrative Update

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Abstract

Annually chronic liver diseases cause two million death worldwide. Although liver transplantation (LT) is still considered the best therapeutic option, the limited number of donated livers and lifelong side effects of LT has led researchers to seek alternative therapies. Tissue engineering (TE) as a promising method is considered for liver repair and regeneration. TE uses natural or synthetic scaffolds, functional somatic cells, multipotent stem cells, and growth factors to develop new organs. Biological scaffolds are notable in TE because of their capacity to mimic extracellular matrices, biodegradability, and biocompatibility. Moreover, natural scaffolds are classified based on their source and function in three separate groups. Hemostat-based scaffolds as the first group were reviewed for their application in coagulation in liver injury or surgery. Furthermore, recent studies showed improvement in the function of biological hydrogels in liver regeneration and vascularity. In addition, different applications of natural scaffolds were discussed and compared with synthetic scaffolds. Finally, we focused on the efforts to improve the performance of decellularized extracellular matrixes for liver implantation.

Keywords Liver regeneration · Tissue engineering · Stem cells · Natural scaffolds · Decellularized extracellular matrices · Hydrogel · Hemostat

Abbreviations

OLT	Orthotopic Liver Transplant
MSCs	Mesenchymal Stem Cells
ESCs	Embryonic Stem Cells
iPSCs	Induced Pluripotent Stem Cells
ECM	Extracellular Matrices
dECM	Decellularized Extracellular Matrices
MACS	Microchanneled Alkylated Chitosan Sponge
PGMs	Porous Gelatin Microspheres
mTG	Microbial Transglutaminase Enzyme
GMA	Gelatin Methacryloyl
HA	Hyaluronic Acid
HAMA	Cross-Linked Methacrylated HA
GHA	Galactosylated HA
EGF	Epidermal Growth Factor
VEGF	Vascular Endothelial Growth Factor
PCL	Polycaprolactone
PEO	Polyethylene Oxide

Introduction

The liver is a vital organ in the human body that plays a crucial role in metabolic homeostasis, xenobiotic metabolism, detoxification, and immune regulation [90]. The total number of chronic liver disease cases is estimated at 1.5 billion worldwide, including nonalcoholic fatty liver disease (59%), hepatitis B virus (29%), hepatitis C virus (9%), and alcoholic liver disease (2%) [14]. The hepatitis B and C viruses are the most common etiologic factors for liver cirrhosis and liver carcinoma [5]. The World Health Organization's statistics reported that 354 million people are infected with these viruses in the world [84] . Annually, viral hepatitis, hepatocellular carcinoma, and complications of liver cirrhosis are responsible for approximately two million death worldwide.

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Hepatocellular carcinoma and cirrhosis were known 11th and 16th-leading causes of death in 2019, respectively [8].

The liver has a unique regeneration capacity, and it can restore mass and function [86]. In critical clinical conditions that the liver couldn't regenerate itself, orthotopic liver transplant (OLT) is the gold standard and known best treatment method for liver failure. However, the limited number of donated livers is one of the most significant obstacles to the broad application of this therapy. Moreover, the use of immunosuppressive drugs causes unwanted side effects and severe microbial infections in these patients.

On the other hand, this surgical procedure causes a high financial burden to the health system and the patient [2]. Another approach is to use extracorporeal liver support devices, which are used for patients on waiting lists for liver transplantation or during the early treatment stages after liver transplantation. The limitations of these devices can refer to restriction in patient's movement, limited processing volumes, the optimum supply of oxygen to cell compounds, and removal of the bile [104]. Tissue engineering could be considered the third modality to reduce the mortality rate due to liver diseases, which does not have these restrictions and is more accessible.

Nowadays, tissue engineering is known promising technology in biomedicine that is developing by using engineering science and biology to repair damaged tissues [4, 48]. TE is the knowledge of new tissue or organ formation from cells, scaffolds, and growth factors. These scaffolds are three-dimensional structures that provide cell growth and a supportive microenvironment for the differentiation and maintenance of cells in ECM [43]. Researchers in tissue engineering science investigate cell implantation by suitable scaffolds, microenvironmental conditions for cell survival, and finally, controlling all factors that contribute to the development of new tissue [34]. In this review, we highlighted natural scaffolds in liver regeneration. In addition, we compared biological scaffolds with synthetic ones used in tissue engineering.

Natural biomaterials

An ideal scaffold should have the following characteristics: biocompatibility, biodegradability with controllable degradation rate, highly porous three-dimensional structure for cell connection, penetration and division to simulate extracellular matrices, suitable mechanical strength to support regeneration, and finally, surface chemistry and topography to improve cellular interactions and tissue growth [67]. Scaffolds are divided into two general groups: synthetic and biological scaffolds. Synthetic polymers are hydrophobic materials with a slow degradation rate in biological conditions due to their high mechanical strength [39]. Many synthetic polymers are used as scaffolds in tissue engineering, and several cases have been specifically designed for skeletal muscle regeneration. Control of physical and chemical properties distinguishes these polymers from natural polymers [115]. These polymers have limitations such as hydrophobicity, low degradation rate, low cell affinity, weak cellular response, acidic byproduct, and unsuitable conditions for drug delivery (H.-S. [62, 64]. The biological scaffolds offer suitable biocompatibility dependent on the material source [44, 83] and do not stimulate the immunity system [3, 103]. These scaffolds can provide environmental conditions similar to extracellular matrices (ECM).

Biological scaffolds are in the spotlight due to the appropriate immune response, mild antigenic properties, angiogenesis, improvement of cellular adherence, and hemostasis [71]. However, natural scaffolds don't support the required mechanical properties of an ideal scaffold for tissue repairing and require modification with other compounds e.g. galactose [33]. Natural scaffolds are usually fabricated in a form such as fiber, powder, 3D printed structures, and sponges. Decellularizing whole tissue or organs also leads to potential natural scaffolds for tissue repair (Fig. 1). In this article, we reviewed the natural platforms used in liver regeneration in three groups: hemostats, hydrogels, and decellularized extracellular matrices (dECM) (Fig. 2).

Hemostat-based scaffolds

In recent years, some studies have focused on the integration of hemostatic properties in the studied scaffolds in tissue regeneration. Because these scaffolds, while preventing bleeding at the injuried site, provide conditions for cell proliferation and differentiation. Therefore, in this review article, homeostatic scaffolds are also considered as an independent section.

High blood loss during liver surgeries is a concerning problem [54]. The hemostat scaffolds have a porous structure that provides conditions for fluid crossing from hemostats. Depleting free water stabilizes the hemostat at the injury site and allows tissue repair by absorbing fluids [61, 126]. The high porosity is an ideal property of homeostatic polymer, which is converted to a unique scaffold in tissue engineering. These structures are usually biocompatible, available, biodegradable, lightweight, and low cost [7, 9, 118, 126]. Biodegradability is one of the main parameters that should consider. Otherwise, if the polymers don't decompose on the target site, they must drain from the wound, which can be painful for the patient [61]. Sometimes designed hemostat polymers don't possess highly interconnected porous structures that lead to poor absorption of blood, so inefficient in controlling bleeding [118].

Chitosan is an excellent candidate for hemostat scaffold synthesis due to with antibacterial and hemostasis properties. Some studies have shown that adding a hydrophobic group to chitosan leads to solid hydrophobic interactions

with the membrane of platelet, red blood cells, and bacteria that improve its anti-infective and hemostasis strength [16, 25, 26]. Chitosan is not much soluble in physiological conditions. Haddad-Mashadrizeh et al. increased its solubility at neutral pH by blending it with sodium glycerol phosphate [40]. Du et al. designed the alkylated chitosan sponge with microchannels (MACS) that absorbed water and blood. Its shape can be rapidly recovered. MACS has a higher capacity in hemostasis and procoagulant properties than commercial hemostats. In situ experimental results indicated successful vascularization, tissue integration, and infiltration of the liver parenchymal cell (Table 1)[27].

Gelatin has benefits similar to other natural materials (Q. [52, 53]. Its most notable feature is activating platelet aggregation that converted it to favorable hemostatic material [66]. Gelatin has a high capacity for blood absorption, which leads to in situ concentrated blood proteins and improved blood clotting [49]. Swelling of gelatin stops bleeding by inducing pressure on the injury site [54]. In recent years, hemostats have been fabricated into forms of sponges, films, webs, silks, and powders [101]. The powder hemostats have always been considered for increasing the contact surface with blood cells [68]. Porous gelatin microspheres (PGMs) showed better hemostatic performance than commercial samples [66]. Fabricated hemostats from gelatin matrix-thrombin, and microbial transglutaminase cross-linked thrombin (TB) loaded Gelatin (mTG/TB/gelatin) reduced clotting time to about one minute [18, 22]. Mushroom tyrosinase and microbial transglutaminase (mTG) were used to crosslink silk fibroin/gelatin that showed a similar result [107]. Three-dimensional gelatin sponges comprised a porous structure with low density, extremely high capacity for absorption of blood and tissue secretions, high surface area, and compressibility, which showed its superiority compared with commercial hemostats, medicine gauze, and gelatin nanofiber membrane (details are shown in Table 1) [116].

Nano or cellulose microfibers have been used widely in tissue engineering [85] and wound healing [108]. Cellulose has a high potential for surface chemical modifications [76] as carboxylation, which improved its absorption and degradation in biological conditions [122]. The blending of oxidized cellulose to the chitosan (CS)/gelatin sponge has improved the hemostatic activity of CS/gelatin (Table 1)[93].

Hydrogel-based scaffolds

Hydrogels are the hydrophobic structure that is insoluble in water. Hydrogels are similar to natural tissue because of their high potential in absorbing a massive amount of biological liquids. In addition, the other advantages of these scaffolds could be referred to as suitable mechanical strength and long life. They have a high potential for carrying cells, drugs, and bioactive compounds. In addition, hydrogels provide an environment for remodeling, migration, and adhesion [79, 99]. Hydrogels keep the wound environment moist and cool and allow oxygen to penetrate, which reduces pain in the patient [124]. Antioxidation, adhesiveness, hemostasis,

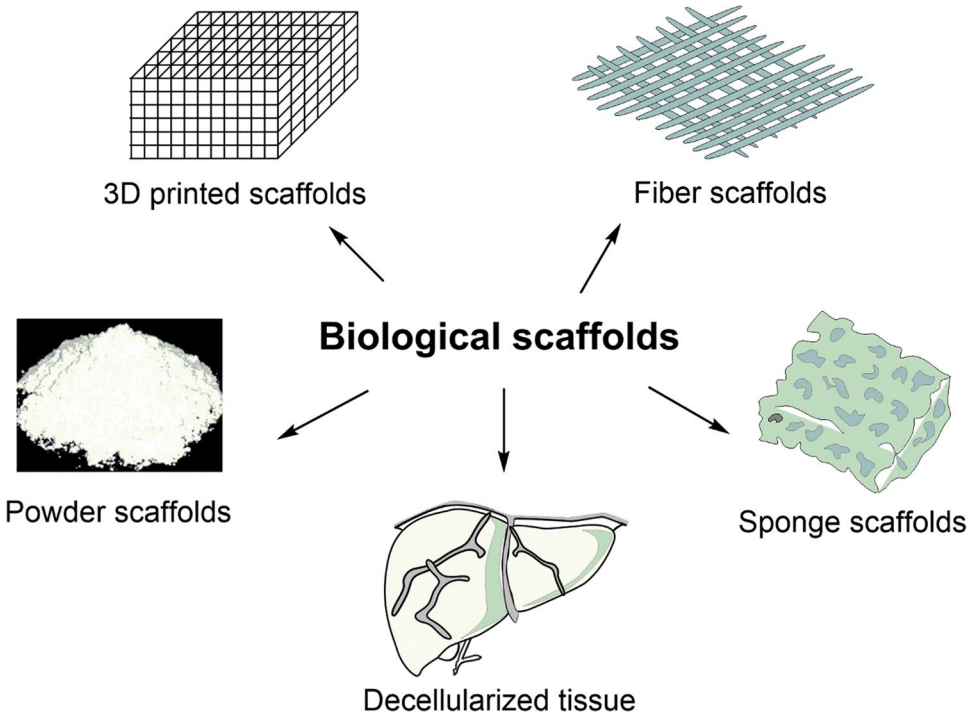

Fig. 1 Natural scaffolds shape: fiber, sponge, powder, 3D printed, and decellularized tissue

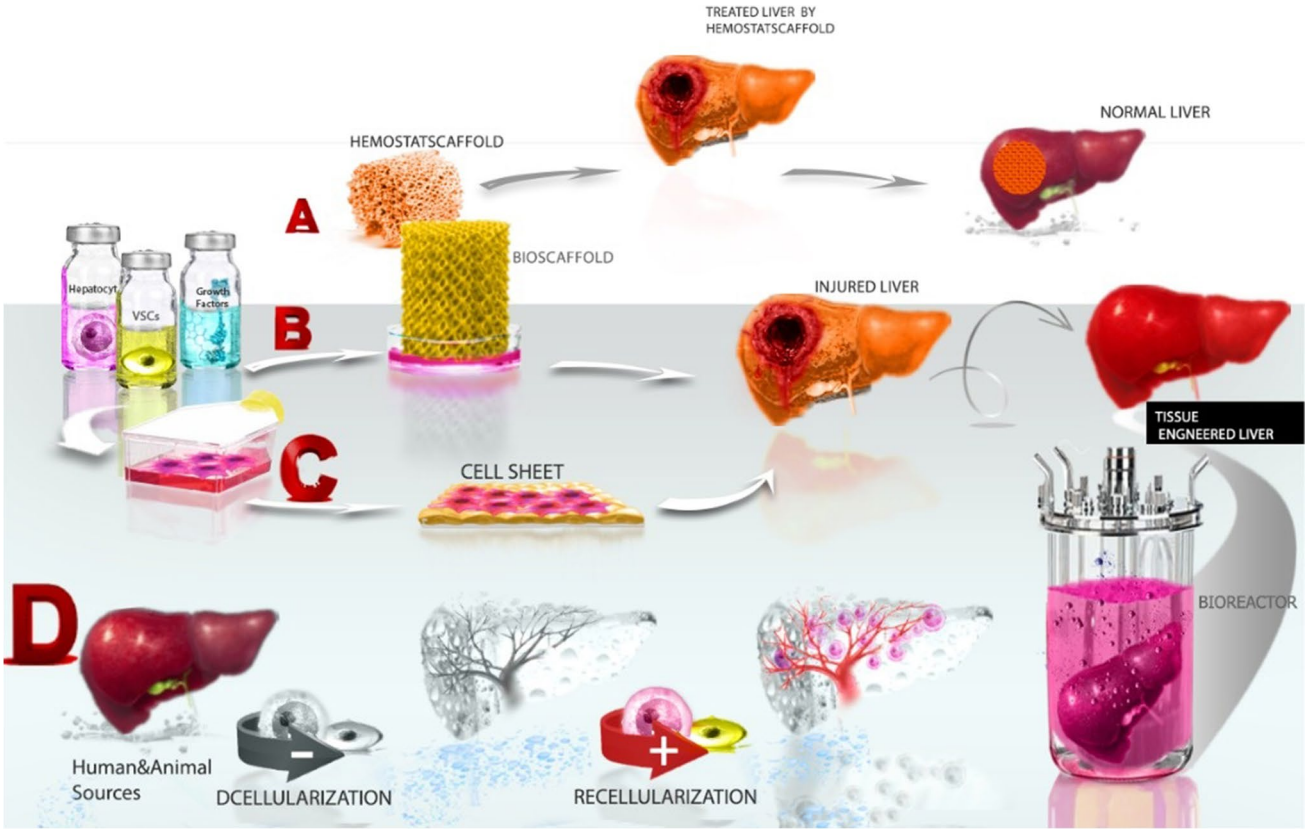

Fig. 2 Comparison of liver reconstruction strategies: **A**) Hemostat scaffolds inhibit bleeding at the injury or surgery site by absorption and coagulation of blood. **B** and **C**) Hepatocytes and endothelial cells are cultured in vitro in the presence or absence of scaffolding, then used in liver regeneration. **D**) Liver tissue originated from humans or animals is decellularized. Hepatocyte and vascular endothelial cells are perfused into the decellularized scaffold. The repopulated scaffold is placed in a bioreactor to prepare whole tissue and complete the vascular network

anti-infection, and drug encapsulation are ideal properties of wound healing hydrogels [36]. Hydrogels structure is impacted by polymer concentration, temperature, pH, cross-linking degree, and salt concentration. These polymers were fabricated by polysaccharides, proteins, synthetic polymers, and their hybrid [79, 99]. Despite the high potential of hydrogels for tissue engineering, their application in medicine has limitations. These limitations include pore size-dependent release rate, limited drug loading capacity, the toxicity of some cross-linker, sensitivity to temperature and pH, low survival of encapsulated cells, and cell damage during photopolymerization [79]. The hydrogels are usually applied for one of the wound types and have limited applicated features [56].

The prepared hybrid hydrogel by Chen et al. significantly improved tissue adhesion, coagulation, hemostasis, and anti-infection in the skin and liver injuries. In addition, the controllable release of VEGF leads to the improvement of cellular proliferation and tissue regeneration (Table 2) [16]. The growth factors have a high affinity for binding to the glycosaminoglycans like heparin, which regulate many of their activities and provide biological stability against proteases activity. The chitosan/galactosylated hyaluronic acid /heparin sponge's ability to carry EGF could improve cell maintenance microenvironment and prolong hepatocyte activities for a long time (Table 2)[32].

Pore size is a limiting factor for cell growth, proliferation, and migration. The photo-cross-linkable gelatin-glycidyl methacrylate was developed from the porous alginate [28] and gelatin methacryloyl (GMA) hydrogels [63], resulting in improving pore size by maintaining mechanical strength (Table 2) [102]. Protease cleavage sites of gelatin lead to its biodegradation during the replacement of new ECM [12]. In addition, the presence of Arg-Gly-Asp sequences gives it the ability to connect to membrane proteins like integrin [70]. However, gelatin-based hydrogels possess weak mechanical and thermal strength as their main limitation [30]. Methylation of lysine residues causes 3D cross-linked polymer formation that is more resistant to temperature [72]. ECM compounds such as hyaluronic acid (HA) can

Table 1 Hemostat-based scaffolds for liver regeneration

Bio-scaffolds	Description of the structure	Experimental results	Advantages	Ref
Chitosan/galactosylated HA/heparin	Highly porous scaffold composed of chitosan and galactosylated hyaluronic acid that filled with heparin	Improvement of cell proliferation along with hepatic functions such as albumin secretion, urea synthesis, and ammonia elimination	Introducing HGF into the scaffold by its high affinity to heparin, long time activity of growth factor interacted with heparin, improved the formation of cell aggregates due to enhanced liver metabolic function	[32]
Chitosan	Four-armed benzaldehyde-terminated polyethylene glycol and dodecyl-modified chitosan hybrid	Promoting of cell proliferation and tissue remodeling in the wound bed; repairment of acute tissue injuries in vessel bleeding and liver bleeding; improvement of angiogenesis, collagen deposition, macrophage polarization, and granulation tissue formation for repairing of the chronic wound in the animal model	Improved tissue adhesion, coagulation, hemostasis in skin and liver, and anti-infection, controllable release of VEGF	[16]
3D Bacterial nanocellulose	3D bacterial nanocellulose using paraffin wax in medium culture	Improvement of cell growth and prevention of cell inhibition	Enhanced cell–cell connections result in improvement of cell proliferation	[85]
Chitosan/dextran	Hydrophobically modified chitosan (hmCS) and oxidized dextran hydrogel	Coagulate heparinized whole blood in vitro and demonstrates of hemostasis activity in a rat hemorrhaging liver model	Anti-infective activity, hemostasis capacity, and improved tissue adhesion	[25]
Porous gelatin microspheres	Prepared with gelatin cross-linked by glutaraldehyde	Better hemostatic performance than commercial hemostats powder due to high porosity in vivo and in vitro	Decreased hemostasis time than commercial hemostats,	[66]
Gelatin/dopamine	Interpenetrating polymer network formed by cross-linked gelatin and dopamin	Improvement whole blood clotting capacity with less blood loss and shorter clotting time into mentioned animal models	Enhancement of coagulation and reduced blood loss in less hemostasis time	[46]
Chitosan	Highly interconnective microchannels of alkylated chitosan by combining 3D printed microfiber	Improvement of water and blood absorption compared with commercial hemostats into mentioned animal models, promotion of angiogenesis, liver parenchymal cell infiltration, and tissue integration into a rat liver defect model	Bioengineering a rapid-shape hemostat with high capacity in the blood absorption, improvement of liver parenchymal cell penetration, and vascular formation ability	[27]
Gelatin/mTG/Thrombin	Microbial transglutaminase (mTG) crosslinked thrombin filled with Gelatin	Improvement whole blood clotting time to one minute, platelet adhesion, and blood absorption in vitro and in vivo	Increased hemostasis time	[18]
Gelatin	Continuous interconnected gelatin nanofibers	platelets aggregation and activation platelets in large quantities to accelerate the formation of platelet and simultaneously amplification other extrinsic and intrinsic coagulation pathways; increased rate of inducing stable blood clots with least blood loss in vivo	Increased absorption of blood result in least blood loss, high cell permeability, with low hemolysis ratio	[116]
Chitosan/gelatin	Chitosan/gelatin composite sponges containing oxidized cellulose fibers cross-linked with tannic acid	Increased the clotting capability, and the bioabsorbability in vivo	Increased swelling ratio and coagulation strength of the sponge due to TEMPO-oxidized cellulose fibers, biocompatibility and higher bioabsorbability of scaffold in rat liver	[93]

compensate for the poor mechanical strength of GMA [111]. Hyaluronic acid is one of the central compounds of ECM in many tissues. It is responsible for tissue formation, wound healing, and morphogenesis. These linear polysaccharides have a high affinity for adhesive receptors, responsible for poor cell adhesiveness [72, 73]. Cross-linked methacrylic HA (HAMA) improved mechanical and chemical properties. Enhance resistance to enzymatic degradation while maintaining biocompatibility. So far, various hybrids of GMA/HAMA have been made [12, 45, 60], but the combination of these two polymers in a ratio of 4:1 had a significant effect on improving its properties [111]. Chitosan/galactosylated HA (GHA) improved hepatocyte cells adhesion while maintaining liver functions. Added hyaluronic acid to gelatin cryogel increased the elastic modulus while decreasing the scaffold toughness, compressive strength, cell growth, and proliferation (Table 2) [55].

Three-dimensional bioprinting is a high-potential approach for the simulation of ECM in tissue engineering via the building of scaffolds. Hydrogels due to the significant similarity to ECM used as bio-inks [78, 94, 97]. The hydrogels such as elastin, agarose, collagen, chitosan, alginate, gelatin, and hyaluronic acid were used in 3D bioprinting. However, they indicated poor printability [51]. Collagen is the most common compound of ECM used in many bioscaffolds structures (A. [62, 64]. Despite the benefits of this biomaterial, such as low mechanical strength, high degradation rate, variable elastic modulus, and viscosity during processing, its usage in bioprinting is limited [74]. A slower degradation rate of chitosan than collagen [23] leads to their simultaneous use as bio-inks in bioprinting, improving their degradation rate and mechanical strength [105, 127]. Sue et al. improved the printability of hybrid collagen/chitosan via the formation of hydrogen bonds and careful temperature control during bioprinting. By changing the presence ratio of each, the bioscaffolds properties could benefit different tissue engineering applications (Table 2) [106]. Chang et al. fabricated volvox spheres with alginate and collagen polymers and encapsulated them with MSCs and AML12 hepatocytes. These 3D scaffolds improved liver repair and regeneration in necrosis liver (Table 2) [13]. Reports indicate the unique role of silk-gelatin bio-ink in cell signalings such as Wnt/β-catenin, bone morphogenetic pathways, and Indian hedgehog play an essential role in liver regeneration [98]. Studies have been shown the successful cultivation of hepatocytes into silk scaffolds. Chitosan presence in these structures reduced inflammatory response [100], while RGD peptide improved gene expression [50]. Co-cultivation of hepatocyte and stellate cells in silk scaffolds promoted hepatic functions [114]. Bioengineering porous silk/extracellular protein scaffold provided conditions for co-cultivation of non-parenchymal cells and primary human hepatocytes [59].

Nano-fibrous structures could act as cellular scaffolds due to are their similarity to ECM [113]. Studies have confirmed that nanofibers and the chemical nature of their structure have significant positive effects on cellular proliferation, growth, migration, and adhesion [15]. However, the application of chitosan nanofibers has been limited due to their high degradation rate and edema [21, 123]. The presence of one synthetic polymer such as polycaprolactone (PCL) [41] or polyethylene oxide (PEO) [20] into chitosan nanofibers leads to improved mechanical strength and processability. However, the synthetic polymers, due to high hydrophobicity properties, reduced cell growth and adhesion [10]. Increased hydrophilicity of scaffolds enhances cell growth and proliferation [120]. Studies have indicated that adding hydrophilic compounds like *Aloe vera* [120], Gum [92], and galactose [37] can enhance hydrophilic groups of scaffolds surface and improve cell adhesion [91].

The importance of 3D shape controlling cellular constructs in tissue engineering led to producing a hepatic lobule-shaped microtissue. These structures were fabricated from capsulated rat liver cells with poly-L-lysine-alginate and have higher hepatic function than spheroids; thus, they could be used as blocks in the bioengineering of liver scaffolds (Table 2) [69]. Yajima et al. simulated a hepatic lobule through assembled cell-laden hydrogel microfiber coated with vascular endothelial cells for liver cells perfusion (Table 2) [117].

Decellularized extracellular matrices-based scaffolds

The biological ECM is prepared from the decellularization of part of the organ or its whole, which its remaining cells made the specific ECM and containing ideal scaffold properties such as complexity, vascular networks, and tissue-specific construction [80, 109]. Stem cells are differentiated based on environmental conditions, which usually don't consider in tissue engineering and tissue repair. Stem cells are often delivered directly into damaged tissue and are ignore tissue biochemistry, needed complexity for 3D scaffold, and vascularity. While tissue repair usually occurs at the wound border, environmental conditions are similar to host tissue [109]. Decellularized ECM (dECM) has tensile strength similar to native tissue and maintains structural integrity. Lack of proper vascular network and primary engraftment transplantation is the most significant limitation in successful tissue engineering [6]. These structures often carry the main vascular branches of origin tissue, which could proliferate and differentiate into the new tissue. Sometimes, they repopulate with endothelial cells or stem cells for new vascular formation [95].

Table 2 Hydrogel-based scaffolds for liver regenertion

Bio-scaffolds	Description of the structure	Experimental results	Advantages	Ref
poly-L-lactic acid fibers	Perfusion bioreactor	73.8% efficiency in perfusion culture of 7 days in the bioreactor, increased albumin production	Maintenance of cell viability and increased albumin production by enhanced nutrient and oxygen diffusion	[88]
Cellulose	Spheroids fabricated in vitro in methylcellulose medium	Increased cell viability and differentiation; significantly increased spheroid-implanted chambers to 16 fold after 45 days	Enhanced cell–cell and cell-matrices interaction liver progenitor cells (LPC)-derived hepatocytes into the spheroid	[119]
Alginate microgels	human-derived liver cells encapsulated in alginate	Increased cell density to 34-fold into spheroids and maintaining cell viability; optimization nutrient and oxygen for achieving to a cell density at harvest	Increased cell viability in aggregates mixed with microgels, enhanced cell proliferation and retained hepatic function	[31]
Multi-component hydrogel fibers	Multi-component hydrogel polyelectrolyte fibers consisted of water-soluble chitin, galactose, collagen and alginate	Facilitated vascular network formation by the presence of endothelial cells in the scaffold when implanted	Bioengineering of hepatic lobule-shaped microtissue (HLSM) containing hiPSCs-derived hepatocytes and endothelial, increased albumin secretion	[24]
Chitosan/hyaluronic acid sponge	Galactosylated chitosan (GCs)/hyaluronic acid (HA) hybrid sponge	Improvement of primary hepatocytes functions such as hepatocyte-specific gene expression, urea production, and testosterone metabolism when co-cultured with endothelial cells	Co-cultivation of endothelial and hepatocyte cells, improved liver-specific functions, and good biocompatibility	[96]
Nylon 12-based perfusion system (poly-L-lactic acid fiber)	A three-dimensional (3D) scaffold comprise 43 culture chambers and human hepatoma Hep G2 and TMNK-1 cells packed into the culture chambers with poly-L-lactic acid fibre	Increased hepatic function and well-maintained cell viability	co-culture of endothelial cells and hepatocytes for bioengineering of a liver with their perfusion	[87]
Volvox sphere	Cells-encapsulated volvox spheres were prepared into premixed alginate/collagen and poly-l-lysine	Differentiation of encapsulated MSCs into hepatocyte-like cells along with increasing albumin and cytokeratin 18 expressions in a dynamic bioreactor, and restoration of the necrotized liver by volvox spheres encapsulated with both stem cells after transplantation into the liver	Regeneration of new liver with normal functions obtained MSCs differentiation	[13]
Poly-L-lysine-alginate	-	Fabricating 3D multilayer hepatic lobule-like with control of tissue shape and higher hepatic function	Bioengineering of hepatic lobule-shaped microtissue (HLSM) containing rate hepatocytes	[69]
Gelatin	Photocrosslinkable gelatin methacryloyl	Provided the condition for cell attachment and promoted intercellular interaction of hepatocytes, which caused improved cell function	Enhanced cell–cell and cell-ECM interactions	[63]
Alginate	Alginate polymer conjugated with GRGDSP peptide	Improvement cell proliferation, hepatic functions, and vascular network formation	Co-culture of endothelial cells and HepG2 cells in a lobule-like scaffold	[117]

Table 2 (continued)

Bio-scaffolds	Description of the structure	Experimental results	Advantages	Ref
Collagen I	Collagen I-coated poly(ethylene glycol) hydrogel scaffold	Organoid formation ability similar to adult tissue with gene expression, protein secretion, drug metabolism, morphology function in vitro, and angiogenesis and viral infection followed by implantation into the injured liver in immune-deficient mice	Improved the formation of hepatic progenitor organoids by the porous scaffold	[82]
Poly(ethylene glycol) diacrylate, gelatin methacrylate, collagen and fibrin hydrogels	Photopolymerizable hydrogels by using food dye additives	Demonstrated intravascular and multivascular formation into 3D structure by exploring the oxygenation and the flow of human red blood cells during tidal ventilation and distension of a proximate airway	Enhanced production of albumin, improvement of the function of hepatic aggregates, co-culture hepatocytes and endothelial cells, 3D printing of vascular scaffolds	[38]
Gelatin/hyaluronic acid	Microporous cryogel scaffold	Reduced production of mesothelium proteins E-cadherin and calretinin in the cryogels in vitro; a mesothelium layer formation similar to the native mesothelium tissue after 21 days implantation the cell/cryogel construct	Bioengineering of a 3D cryogel scaffold for mesothelial cells culture, adverse effect of incorporation of HA into gelatin at cell proliferation, cell morphology, cytoskeleton arrangement, and reduced specific genes expression of mesothelial cells	[55]
Hydrocaffeic acid-modified chitosan/hmCS lactate		Investigation of cytotoxicity, the biocompatible and biodegradable of the hydrogel in vivo	Biocopatible, biodegradable, anti-infective, and non-toxic	[26]
Gelatin-glycidyl methacrylate		Improved cellular functions such as differentiation, viability, and proliferation	Improved pore size; improved cellular functions such as differentiation, viability and proliferation	[102]
Chitosan-β-glycerol phosphate hydroxyethyl cellulose		Detection of injected cells at the target organ for 6 months in both scaffold and scaffold-free groups; reduced cell migration into other organs by scaffold	Reduced cellular escape from transplantation site, improved cell viability, and enhanced scaffold solubility in physiological conditions	[40]
Collagene	3D collagen matrix scaffolds	adhesion and differentiation of Human mesenchymal stem cells (hMSCs) into chondroblasts, osteoblasts, and adipocytes,	novel strategy for tissue regeneration without affecting their differentiation capacity	[65]

Table 3 Decellularized extracellular matrices-based scaffolds for liver regeneration

Bio-scaffolds	Cell lines	Animal model	Experimental results	Advantages	Ref
Decellularized rat whole liver	Primary rat hepatocytes	Lewis rats with unilateral, nephrectomy	Efficient recellularization of the liver matrix with adult hepatocytes and hepatic functions including albumin secretion, urea synthesis and cytochrome P450 expression at comparable levels to the normal liver in vitro; its transplantion into rats	Maintenance of cell viability and hepatic functions, successful vascularization after perfusion of endothelial cells	[110]
Decellularized rat cadaveric liver lobes coated heparin	Primary rat hepatocytes	Lewis rats	Didn't observe any thrombosis; prolonged survival of rats and promoted hepatic functions	Elimination of thrombosis by coating heparin: promoting of liver function	[6]
Decellularized mouse liver scaffolds	Mouse bone marrow-derived mesenchymal stem cells	NOD-SCID mice	Improvement of hepatic function in vitro and its maintenance after implantation into injured liver	Improved liver functions and differentiation of MSCs into hepatocytes	(W.-C. [52, 53]
Decellularized piglet's whole liver conjugated Rat anti-mouse CD31 antibody	Vascular endothelial cells (MS1)	Normal Yorkshire pigs (female)	Same endothelial attachment and significantly reduced platelet adhesion against blood perfusion in vitro; support and maintenance of physiological blood flow up to 24 h in vivo	Vascularized bioengineering of whole liver through conjugation of CD3 antibody for enhancement of vascular endothelial cells proliferation	[58]
Decellularized rat whole liver scaffolds	Porcine iPSCs	Sprague–Dawley rats	Scaffold structure and hepatic functions after implantation, while coagulation after 1–2 h of blood reperfusion	Promoted hepatic differentiation of iPSCs, maintenance of hepatic functions, coagulation in about 1–2 h after heparin injection	[89]
Decellularized porcine whole liver coated heparin gelatin	Human EA. hy926 endothelial cells and HepG2 cells	Hybrid pigs	Efficiently endothelialized vascular trees without thrombosis and improved hepatic functions in vitro and in vivo	Improvement vascularized by enhancement of endothelial recellularization; co-culture hepatocyte and endothelial cells	[47]
Decellularized mouse whole liver scaffolds	Neuro-glia antigen 2, hematopoietic progenitor cells	C57BL/6 mice with liver Cirrhosis and right nephrectomy	Promoting hepatic differentiation of HPCs in vitro; excellent restoration of hepatic functions after implantation of cell-loaded scaffolds than that with the injection of cell suspensions in the rat	High regeneration rate of liver integrity and function after transplantation	[121]
Rat decellularized liver	Human induced pluripotent stem cells (hiPSCs)	-	Distribution of the hiPSC-HLCs of the recellularized liver into the parenchymal space after 48 h of continuous perfusion culture, albumin and CYO3A4 expressions and albumin secretion into the culture medium	Bioengineering of artificial scaffold for differentiation and proliferation of hiPSCs	[75]

Table 3 (continued)

Bio-scaffolds	Cell lines	Animal model	Experimental results	Advantages	Ref
Decellularized rat liver scaffolds	Human EpCAM liver cells	Wister rate	maintenance of cell proliferation and enhanced hepatic functions in vivo; improved survival of rats and maintenance of hepatic functions	Using decellularized scaffolds to restoring liver functions	[112]
Porcine liver ECM coated with chitosan (CTS) fabrics	C3A human hepatocytes	-	Promoting cell bioactivity and liver-specific function, such as albumin secretion and urea synthesis, compared with those cultured on untreated scaffolds	Bioengineering of CTS-ECM scaffolds for increased viability and functionality of hepatocytes	[125]
Decellularized rat whole liver/silk gelatin 3D printed scaffold	Mice hepatocyte	-	Increased proliferation until 2 weeks; upregulation asialoglycoprotein receptor 1 (ASGR1) hepatic marker, β-catenin expressions and downregulation of EpCAM expression; albumin production	Bioengineering 3D printed scaffold for maintenance of differentiation and metabolic functions of hepatocytes through activation of the Wnt/β-catenin signaling pathway	[98]
Decellularize rat livers	induced pluripotent cells (iPSCs)	Male albino rats	Upregulation of Wnt/β-catenin pathway, growth factors, and liver specification genes; restored liver-specific functions including albumin secretion and urea synthesis	Bioengineering a 3D-organ scaffold that can be used to transplantation using iPSCs recellularizaton; raised iPSCs differentiation into hepatocytes due to upregulation of Wnt/β-catenin pathway	[29]
Rat liver acellular scaffolds	human liver stem cells (HLSC)		HLSC lost the embryonic markers (alpha fetoprotein, nestin, nanog, sox2, Musashi1, Oct 3/4 and pax2), increased the expression of albumin, acquired the expression of lactate dehydrogenase and three subtypes of cytochrome P450; production of urea, expression of cytokeratin-19, CD31 and vimentin in cells attached to tubular remnant matrix structure	Provided a favorable environment for differentiation of HLSC in functional hepatocytes; promoted the generation of some epithelial-like and endothelial-like cells	[81]
Decellularized Wistar rat livers pre-coated with HepG2-conditioned medium (CM)	Human induced pluripotent stem cells (hiPSCs)-derived mesenchymal cells (hiMSCs), and HepG2 and endothelial (HAEC) cells		Improved the quality of liver ECM matrices, adhesion, spreading and proliferation	High improvement of liver recellularization by pre-coating with HepG2-CM	[11]
Decellularized whole human and rate liver with difference age	Primary rat and human hepatocytes,		Changed ECM with age and significant effect on cell function		[1]

Table 3 (continued)

Bio-scaffolds	Cell lines	Animal model	Experimental results	Advantages	Ref
Decellularized porcine liver extracellular matrix powder at combination of chitosan/gelatin (CG)			Increased ECM concentration that produced a larger pore size, better cytocompatibility, enhanced hemostatic effects, biocompatibility, and wound healing	Limitation of the clotting time to less than one minute	[17]

Table 4 A review of natural scaffolds clinical trial used in liver disease

NCT number	Title	Condition	Intervention	Sponcer/ Collaborator	Phases
NCT02786017	The Safety and Efficacy Assessment of Injectable Collagen Scaffold™ Combined With Human Umbilical Cord-derived Mesenchymal Stem Cells (HUC-MSCs) Transplantation in Patients With Decompensated Cirrhosis	Decompensated Cirrhosis	Injectable Collagen Scaffold + HUC-MSCs	Chinese Academy of Sciences	Phase II
NCT01335568	Intracorporeal Autologous Hepatocyte Matrix Implant: A New Tissue Engineering Procedure for Treatment of Hepatic Disease	Liver Cirrhosis; Liver Insufficiency; Chronic Liver Disease	Hepatocyte Matrix Implant	Baermed	Phase I
NCT02204930	A Multi-centre, Open-label, Uncontrolled, First-in-Human Study to Evaluate the Safety and Tolerability and Explore the Efficacy of PeproStat in Gelita-Spon® Gelatin Sponge in Subjects Undergoing Open Liver Resection Surgery	Hemorrhage	Surgicel® absorbable Haemostat	Haemostatix Ltd	Phase I
NCT01436721	The Randomized Clinical Trial of Surgicel® Absorbable Haemostat Covering the Raw Cut Surface During the Hepatectomy	Liver Neoplasms	Surgicel® absorbable Haemostat	Fudan University	Phase I & II

Liver dECM has been studied (Table 3) as a scaffold for proliferation and differentiation of stem cells, endothelial cells, and hepatocytes for the new liver formation and, finally, its transplant (Table 2). Another application of these scaffolds is their use as a liver disease model, which has led to a better understanding of its role in liver fibrosis and discovering new methods for fibrosis therapy by stem cells [57].

The liver-derived ECM was used for liver injuries treatment, but this type of ECM has low mechanical strength [42]. Therefore, the gelatin/PCL/ECM [10] could be a good scaffold in tissue engineering due to the high potential of gelatin in tissue regeneration [128]and the mechanical strength of PCL [77]. Collagen identifies as a central compound of dECM, which leads to in situ clotting. Collagen-coated with heparin in the dECM scaffold was able to give it anticoagulant properties [6]. Also, the heparin-gelatin mixture has been effective in angiogenesis [47]. Anti-endothelial cell antibodies conjugation in dECM causes the proliferation of vascular cells, and it can develop the vascular network in the scaffold structure [58].

Conclusion

Liver transplantation is yet the best option for treating liver failure. However, due to the limited number of liver donors, an alternative method to diminish liver disease mortality is necessary. Over the past few decades, research in the area of xenotransplantation has progressed dramatically. However, cross-species pathogen infectivity and immunological response to the transplanted tissue are the main problems of this type of transplant [19, 35]. Also, traditional cell therapies perfused stem cells directly in vivo, which has led to poor cell engraftment and a low cell viability rate. Hepatocytes function and survival are dependent on cell–cell interaction and connection to ECM compositions. Natural scaffolds can be used as a supportive platform for cell growth, proliferation, and differentiation. Biological scaffolds are biodegradable, decomposing in physiologic conditions, and are replaced with new extracellular matrices. These structures can also simulate cell physiological conditions, which lead to cell growth and differentiation, and finally, liver regeneration. Studies indicated that these scaffolds could simultaneously cultivate two cells type, hepatocytes, and vascular endothelial cells, which caused vascular network formation and finally provided necessary nutrients and oxygen for newly regenerated tissue. Due to their ability to carry drugs and growth factors, they also play a role in regeneration and rescue the liver. Some of them are in a clinical trial for liver disease treatment (Table 4).

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