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## Novel alternative transplantation therapy for orthotopic liver transplantation in liver failure: A systematic review

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### Abstract

#### BACKGROUND

Orthotopic liver transplantation (OLT) is the only treatment for end-stage liver failure; however, graft shortage impedes its applicability. Therefore, studies investigating alternative therapies are plenty. Nevertheless, no study has comprehensively analyzed these therapies from different perspectives.

#### AIM

To summarize the current status of alternative transplantation therapies for OLT and to support future research.

#### METHODS

A systematic literature search was performed using PubMed, Cochrane Library and EMBASE for articles published between January 2010 and 2018, using the following MeSH terms: [(liver transplantation) AND cell] OR [(liver transplantation) AND differentiation] OR [(liver transplantation) AND organoid] OR [(liver transplantation) AND xenotransplantation]. Various types of studies describing therapies to replace OLT were retrieved for full-text evaluation. Among them, we selected articles including *in vivo* transplantation.

#### RESULTS

A total of 89 studies were selected. There are three principle forms of treatment for liver failure: Xeno-organ transplantation, scaffold-based transplantation, and cell transplantation. Xeno-organ transplantation was covered in 14 articles,

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scaffold-based transplantation was discussed in 22 articles, and cell transplantation was discussed in 53 articles. Various types of alternative therapies were discussed: Organ liver, 25 articles; adult hepatocytes, 31 articles; fetal hepatocytes, three articles; mesenchymal stem cells (MSCs), 25 articles; embryonic stem cells, one article; and induced pluripotent stem cells, three articles and other sources. Clinical applications were discussed in 12 studies: Cell transplantation using hepatocytes in four studies, five studies using umbilical cord-derived MSCs, three studies using bone marrow-derived MSCs, and two studies using hematopoietic stem cells.

### CONCLUSION

The clinical applications are present only for cell transplantation. Scaffold-based transplantation is a comprehensive treatment combining organ and cell transplantations, which warrants future research to find relevant clinical applications.

**Key words:** Cell transplantation; Liver transplantation; Organ transplantation; Xenotransplantation; Tissue engineering; Scaffold

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**Core tip:** This systematic review analyzes the current status of transplantation treatments in place of liver organ transplantation from multiple viewpoints. We classified reports into three types: Xeno-organ transplantation, scaffold-based transplantation, and cell transplantation. Clinical application occurred for cell transplantation with hepatocytes and mesenchymal stem cells; however, the effect was limited. On the other hand, scaffold-based transplantation is a comprehensive treatment that combines organ transplantation and cell transplantation. Future research for clinical application is expected. The present article provides researchers with a summary and updated information on recent trends in alternatives to liver transplantation and support for future research.

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## INTRODUCTION

Liver diseases lead the causes of mortality worldwide, accounting for approximately 1-2 million deaths per annum according to the World Health Organization<sup>[1]</sup>. Orthotopic liver transplantation (OLT) remains as the only curative therapy for end-stage liver diseases. However, the shortage of donor organs limits its application.

Alternatives to OLT such as liver support systems, including bioartificial livers, and hepatocyte transplantation have been extensively explored; however, none could be adopted in clinical practice<sup>[2]</sup>. Thus, to overcome the organ shortage, many researchers attempted to find alternatives to the traditional solid-organ transplantation method<sup>[3]</sup>.

Various alternative treatments are available, including organ transplantations from other human beings, transplanting cells from other species, or transplanting processed cells from humans or transplanting processed cells from other species.

Alternative therapies investigated in the past include xenotransplantation, scaffold-based transplantation, and cell transplantation therapies. In particular, the use of animal livers for human patients, *i.e.*, xenotransplantation, has been deemed as a solution for donor shortage. If the organ of other species could be transplanted, there are many advantages about the supply of organ<sup>[4]</sup>. Although this approach has still several problems, such as immune rejection and coagulopathy,  $\alpha$ -1,3-galactosyltransferase gene-knockout (GT-KO) pigs that do not express the  $\alpha$ 1,3Gal (Gal) antigens have improved the potential of this therapy<sup>[5,6]</sup>. In fact, it underwent many advancements through genome editing technologies<sup>[7]</sup>.

Scaffold-based transplantation is a novel method, which aims to generate tissues

and organs *ex vivo* or *in vivo* with biological materials that can be used to repair, regenerate, or even replace malfunctioning tissues and organs. Essentially, to create scaffolds, all the cells from animal organs are removed while retaining the structural, mechanical, and chemical attributes of the native tissue<sup>[8]</sup>. Then, the human-derived cells are embedded in the scaffold that serves as an ideal container to generate humanized organs.

In parallel, cell transplantation research has undergone vast advancements with the establishment of induced pluripotent stem cells (iPSCs). Clinical human-to-human hepatocyte transplantation following host conditioning has been reported<sup>[9]</sup>. However, hepatocytes have limitations with respect to proliferation, function, and immunity. Recently, pluripotent or somatic stem cells were used as new sources in place of hepatocytes<sup>[10]</sup>. Further, researchers tried to direct pluripotent or somatic stem cells toward differentiation into hepatocytes in various studies<sup>[11]</sup>.

Thus, alternative therapies manifest various combinations depending on different resources. Still, no study has comprehensively analyzed these different viewpoints yet, although such studies are instrumental while considering novel alternatives for the future regarding the utility of these kinds of treatments.

Therefore, we aimed to discuss the current status of alternative transplantation therapies to replace liver organ transplantation and to support their research and development.

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## MATERIALS AND METHODS

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The methodological approach included the development of selection criteria, defining the search strategies, assessing the study quality, and abstracting the relevant data. The PRISMA statements checklist for reporting a systematic review was followed<sup>[12]</sup>.

### **Identification and selection of the studies**

This systematic literature review was performed to select articles discussing alternatives to liver organ transplantation. The PubMed, Cochrane Library, and EMBASE were electronically searched for articles published between January 2010 and December 2018, using the following MeSH terms: [(liver transplantation) AND cell] OR [(liver transplantation) AND differentiation] OR [(liver transplantation) AND organoid] OR [(liver transplantation) AND xenotransplantation].

### **Inclusion and exclusion criteria**

The study selection criteria were defined before initiating data collection to identify eligible studies for the analysis. Only studies written in English were selected. We retrieved all studies in which the primary objective was to evaluate new transplantation therapies in place of OLT for our analysis.

Exclusion criteria were as follows: (1) Studies not including *in vivo* transplantation; (2) Studies lacking sufficient details; (3) Review articles; (4) Expert opinions; (5) Letters; and (6) Conference summaries.

### **Study selection and quality assessment**

The titles and abstracts of the retrieved studies were independently and blindly screened for relevance by two reviewers (Furuta T and Furuya K), who assessed the study quality and extracted data. To enhance sensitivity, records were removed only in case both reviewers judged them to be inappropriate. All disagreements were resolved by discussion and consensus. The study design, quality, level of evidence, and the relevance of the studies were analyzed according to the objective of this study.

### **Analysis**

We classified the reports into three types: Xeno-organ transplantation, scaffold-based transplantation, and cell transplantation. Further, we categorized the source of donor or donor species, recipients, and the clinical applications.

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## RESULTS

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### **Literature search and selection**

The combined search identified 2821 articles. Of these, 2630 were removed after evaluating the title and abstract. By checking the full text, 89 articles were considered eligible for the systematic review and were analyzed qualitatively and quantitatively. The entire study selection process is summarized in **Figure 1**.

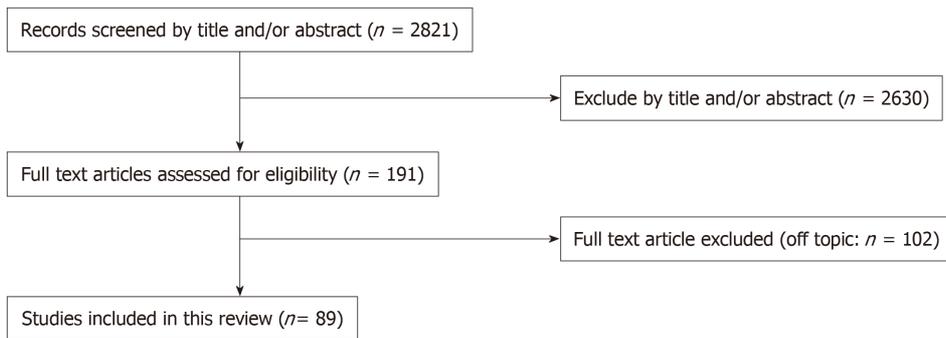


Figure 1 Flowchart of the study selection.

### Treatment modalities and clinical application

From our qualitative analysis on the selected articles, there were 14 xeno-organ transplantation studies, 22 scaffold-based transplantation studies, and 53 cell transplantation studies. The study selection is displayed in Tables 1-3<sup>[2,5,13-99]</sup>. There were various sources of alternative therapy, including organ liver (25 studies), adult hepatocytes (31 studies), fetal hepatocytes (three studies), mesenchymal stem cells (MSCs; 25 studies), embryonic stem cells (ESCs; one study), and iPSCs (three studies) and others (Table 4)<sup>[2,5,13-45,48-70,72-99]</sup>. Clinical application was discussed in 12 studies. In particular, hepatocyte transplantation was discussed in four studies, umbilical cord derived MSCs (UC-MSCs) transplantation was described in five studies, bone marrow derived MSCs (BM- MSCs) was described three studies and hematopoietic stem cells was described two studies.

## DISCUSSION

Among various alternative OLT therapies, only cell transplantation has been adopted in clinical practice. However, its long-term improvement effects are yet to be proven. In particular, few studies report that it can become a bridge for OLT. Considering the viewpoint of cell transplantation, cell processing strategies such as proliferation or hepatic differentiation might assume paramount significance. On the other hand, although scaffold-based transplantation is far from being applied clinically, it is deemed as attractive and promising. This approach has been devised as a treatment method that combines the efficiency of solid organ transplantation with the control of rejection. It is also a comprehensive treatment incorporating cell processing technologies.

Although many patients die from liver failure, there is no other curative treatment other than OLT. However, organ shortage remains as the major shortcoming for transplantation globally. Because of graft shortages, alternative treatments for OLT have received significant research attention.

The concept of scaffold-based transplantation was developed to substitute for the damaged human liver requiring immediate transplantation. In particular, many studies discussed xeno-organ transplantation using decellularized liver scaffolds from other species embedded with human derived hepatic cells.

Our search revealed articles on xeno-organ transplantation ( $n = 14$ ), scaffold-based transplantation ( $n = 22$ ), and cell transplantation ( $n = 53$ ), with the majority being related to "cell therapy".

### Cell transplantation

Cell transplantation is an attractive alternative to conventional organ transplantation. Hepatocyte transplantation has also been applied clinically, however, with limited effect. To obtain better transplantation efficiency, studies were conducted to evaluate the differentiation quality and administration methods.

In this study, regarding transplantation cell sources, we found that adult hepatocytes, fetal hepatocytes, stem cells such as iPSCs, ESCs, MSCs, and differentiated hepatocytes-like cells (HLCs) have been used and most report used hepatocytes as the cell source. In addition, our article showed that only cell transplantation was clinically applied.

Lee *et al*<sup>[13]</sup> reported the application of neonatal hepatocytes encapsulated in alginate microbeads transplanted in three patients with acute liver failure from error of sulfite metabolism. Hansel *et al*<sup>[100]</sup> reported hepatocyte transplantation applied in 100

Table 1 Cell transplantation

Donor						
Cells	Species	Treatments [co-culture (Co), organoid generated]	Recipients (disease, strain etc.)	Outcomes	Year	
Hepatocytes	Human	-	Human (ALF)	Hepatic function	2018 <sup>[13]</sup>	
		-	Human (ACLF)	Hepatic function	2014 <sup>[22]</sup>	
		-	Human (metabolic disease)	Engraftment, hepatic function	2012 <sup>[23]</sup>	
		-	Human (oxalosis)	Hepatic function	2012 <sup>[24]</sup>	
		-	Rat (SD)	Hepatic function, survival extension	2017 <sup>[25]</sup>	
		-	Mouse (NOD/SCID)	Alb secretion, engraftment	2017 <sup>[26]</sup>	
		-	Mouse (FRG)	Engraftment, hepatic function	2013 <sup>[27]</sup>	
		-	Mouse (SCID/Alb-uPA)	Analysis of NK cell	2010 <sup>[28]</sup>	
		UC-MSC (human)	Mouse (BALB/c)	Engraftment, hepatic function	2018 <sup>[29]</sup>	
		Rat	-	Mouse (C57BL/6 FRG)		2018 <sup>[30]</sup>
	-		Rat (Wistar)	Engraftment	2015 <sup>[31]</sup>	
	-		Rat (SD)	Engraftment, hepatic function	2015 <sup>[32]</sup>	
	-		Rat	Engraftment	2014 <sup>[33]</sup>	
	-		Rat (DPP4-)	Engraftment, repopulation	2014 <sup>[34]</sup>	
	-		Rat (An alb)	Engraftment, hepatic function	2014 <sup>[35]</sup>	
	HSCs (Rat), SECs (Rat)/Co		Mouse (C57BL/6)	Engraftment, survival extension	2014 <sup>[36]</sup>	
	-		Rat (SD)	Hepatic function	2010 <sup>[37]</sup>	
	Mouse		Organoid	Mouse (C57BL/6)	Engraftment	2017 <sup>[38]</sup>
			-	Mouse (emdr2 <sup>-/-</sup> )	Engraftment, Repopulation	2015 <sup>[39]</sup>
		-	Mouse (Fah <sup>-/-</sup> )	Hepatic function	2010 <sup>[40]</sup>	
-		Mouse (FVB/N)	Engraftment, analysis of metabolite	2010 <sup>[41]</sup>		
-		Mouse (C57BL/6)	Engraftment	2010 <sup>[42]</sup>		
Hepatocytes (fetal)		Rat	-	Rat (DPPIV <sup>-</sup> )	Engraftment, repopulation	2018 <sup>[43]</sup>
		Mouse	-	Mouse (C57BL/6)	Engraftment, hepatic function	2012 <sup>[44]</sup>
Liver cells		Rabbit	-	Rabbit (New Zealand)	Hepatic function	2012 <sup>[45]</sup>
Hepatic oval cells	Rat	-	Rat (Lewis)	Hepatic function, survival extension	2013 <sup>[46]</sup>	
Hepatoma cell line		-	Rat (SD)	Hepatic function, survival extension	2013 <sup>[47]</sup>	
UC-MSCs	Human	-	Human after OLT	Hepatic function, intervention rate	2017 <sup>[48]</sup>	
		-	Human after OLT	Hepatic function	2017 <sup>[49]</sup>	
BM-MSCs/BM-MNCs	Human	-	Human (LC)	Hepatic function	2017 <sup>[50]</sup>	
		-			2016 <sup>[51]</sup>	
		-	Human (Liver failure)	Hepatic function	2013 <sup>[52]</sup>	
		-	Rabbit	Remodeling	2011 <sup>[53]</sup>	
BM-MSCs/HSCs	Human	-	Human (EPP)	Engraftment	2010 <sup>[54]</sup>	
BM-MSC	Human	-	Human (LC)	Engraftment, hepatic function	2011 <sup>[55]</sup>	
		-	Rat (Wistar)	Hepatic function	2014 <sup>[56]</sup>	
		-	Mouse (SCID)	Engraftment, analysis of glucose	2017 <sup>[57]</sup>	

		-	Mouse (Pfp/Rag2 <sup>-/-</sup> )	Engraftment	2010 <sup>[58]</sup>
	Rhesus macaque	-	Mouse	Hepatic function	2018 <sup>[59]</sup>
	Rat	-	Rat (SD)	Hepatic function	2014 <sup>[60]</sup>
BM-MNC-EPC	Rat	-	Rat (SD)	Remodeling	2012 <sup>[61]</sup>
Liver-MSCs	Human	-	Mouse (NOD/SCID)	Engraftment, repopulation	2011 <sup>[62]</sup>
AD-MSCs	Human	-	Mouse (c57/B6)	Analysis of IRI	2014 <sup>[63]</sup>
	Mouse	-	Mouse (Swiss CD1)	Repopulation	2012 <sup>[64]</sup>
AD-MSC-Hep	Mouse	-	Mouse (C57BL/6)	Engraftment	2015 <sup>[65]</sup>
CD34+ cells	Human	-	Human (LC)	Hepatic function	2015 <sup>[66]</sup>
ESCs-Hep	Mouse	-	Mouse (BALB/c)	Engraftment, hepatic function	2012 <sup>[67]</sup>
iPSC-Hep	Human	Organoid	Mouse (Alb-Tk-NOG)	Survival extension, hepatic function	2017 <sup>[68]</sup>
		Organoid	Mouse (NOD/SCID)	Engraftment	2013 <sup>[69]</sup>
	Mouse	-	Mouse (Fah <sup>-/-</sup> C57Bl/6)	Engraftment	2010 <sup>[70]</sup>
iMPC-Hep	Human	-	Mouse (FRG)	Engraftment	2014 <sup>[71]</sup>
GPSCs-Hep	Mouse	-	Mouse (Hfe-null)	Engraftment	2015 <sup>[72]</sup>
Liver stem cells	Rat	Organoid	Rat (Fah <sup>-/-</sup> Il2rg <sup>-/-</sup> )	Engraftment, hepatic function	2016 <sup>[73]</sup>

“-” means negative treatment. ALF: Acute liver failure; ACLF: Acute on chronic liver failure; SD: Sprague dawley; UC-MSCs: Umbilical cord deriver mesenchymal stem cells; BM-MSCs: Bone marrow derived mesenchymal stem cells; MNCs: Mononuclear cells; HSCs: Hematopoietic stem cells; LC: Liver cirrhosis; EPP: Erythropoietic protoporphyria; BM-MNC-EPC: BM-MNC derived endothelial progenitor cell; AD-MSCs: Adipose derived MSCs; IRI: Ischemia-reperfusion injury; AD-MSC-Hep: AD-MSC derived hepatocyte; iMPC: Induced multipotent progenitor cell; GPSCs: Germ line cell-derived pluripotent stem cells.

patients with errors of metabolism and acute-on-chronic liver failure (ACLF). Nevertheless, the use of human hepatocytes has limitations including limited organ availability, limited cell proliferation, loss of function, and risk for immune rejection<sup>[101,102]</sup>. Previous studies have explored the application of not only hepatocytes but other cell sources as well. Xue *et al.*<sup>[103]</sup> performed a meta-analysis of cell transplantation for ACLF including nine RCTs. In this report, UC-MSCs and bone marrow-derived MSCs (BM-MSCs) were used as the cell source, which improved the survival period and liver function.

MSCs, especially BM-MSCs, have shown immunomodulatory and antifibrotic effects in other organ systems, and MSC transplantation has shown positive results in the treatment of liver fibrosis<sup>[104,105]</sup>. We also found 2 reports of hematopoietic stem cell transplantation, but they were relatively less applied than UC-MSCs and BM-MSCs.

Most importantly, MSCs can secure more sources than hepatocytes, but the problem of cell quality still remains. As a stem cell therapy, iPSCs attract considerable attention in the field of transplantation. iPSCs were established from adult fibroblasts by introducing dierent transcription factors<sup>[106]</sup>. They overcame the ethical aspects of ESCs and have the self-renewal properties and pluripotency, the ability to differentiate into various somatic cells, including hepatocytes<sup>[107]</sup>.

HLCs derived from human iPSCs have been researched as a potential alternative to hepatocytes for cell therapy, disease models, and evaluating drugs<sup>[108,109]</sup>

Takebe *et al.*<sup>[3]</sup> succeeded in creating a liver bud with iPSCs derived HLCs. This study demonstrated a three-dimensional liver bud produced by co-culturing with Human Umbilical Vein Endothelial Cells and MSCs was able to improve the liver function of recipient following transplantation.

A 3 dimensional (3D) culture is effective for hepatocyte functionality<sup>[110]</sup>, and using a method combining iPSCs and 3D culture may eventually assure high cell quality and quantity.

Nevertheless, because of potential tumorigenicity, the risks of developing teratomas, and the lack of long-term safety and ecacy, 3D cultures and iPSCs have not been clinically applied yet<sup>[111,112]</sup>. In our search, we did not find many studies elucidating the *in vivo* application of iPSCs.

Cell transplantation also suffers from these above-mentioned challenges. Moreover, in the recent years, *in vitro* expansion of human hepatocytes has been explored<sup>[113]</sup> to overcome the challenges with iPSCs. The improvements in these approaches may lead to the development of alternative therapies.

### Xeno-organ transplantation

Table 2 Xeno-organ transplantation

Donor organ	Recipients	Outcomes	Year
GTKO pig	Tibetan macaques	Cytokine profile	2017 <sup>[74]</sup>
	Baboon	Survival extension	2018 <sup>[5]</sup> ; 2017 <sup>[14]</sup> ; 2014 <sup>[75]</sup> ; 2012 <sup>[76]</sup> ; 2010 <sup>[77]</sup>
		Analysis of thrombotic microangiopathy	2016 <sup>[78]</sup>
		Analysis of platelet	2014 <sup>[79]</sup>
		Analysis of rejection	2012 <sup>[80]</sup>
		Platelet aggregation	2012 <sup>[81]</sup>
		Analysis of coagulopathy	2012 <sup>[82]</sup>
		Hepatic function	2010 <sup>[83]</sup>
Pig	Baboon	Analysis of immunoglobulin	2018 <sup>[84]</sup>
Rabbit	Porcine, rabbit	Analysis of IgG	2012 <sup>[85]</sup>

GTKO: Alpha 1-3 galactosyltransferase gene knockout; IgG: Immunoglobulin G.

The first successful animal-to-animal liver xenotransplantation was reported in 1968<sup>[144]</sup>. Because of the development of immunosuppressive drugs, various studies were conducted that targeted the applicability of harvested organs from other species. Among animals, pigs were proved as useful in terms of size and rejection strength; therefore, genetically modified porcine organs hold enormous potential for this purpose. Although the cornea and skin of pig have been clinically applied, for OLT, the survival period is so short that liver xenotransplantation could not be applied clinically. To solve the problem of severe rejection, GT-KO pig was developed, intending to reduce the risk of GVHD<sup>[115]</sup>. The recent development of CRISPR/Cas9 has made this animal model more suitable<sup>[116]</sup>.

Regarding xenotransplantation, 12 of 14 articles in our search used GT-KO pigs. Shah *et al*<sup>[14]</sup> reported that a human prothrombin-concentrate complex and immunosuppression was used on GT-KO pigs and that the survival was improved. Even then, it is necessary to improve physiological problems such as rejection, coagulation factors, and complementary species specific for application in humans.

### Scaffold-based transplantation

Regarding rejection and infection, decellularization of tissue is an attractive method. Decellularization of tissues and even whole organs represents a novel approach for developing perfusable extracellular matrix (ECM)-derived scaffolds with preserved vascular integrity. Decellularized tissue is rarely rejected and is used for tissue reconstruction as scaffold material<sup>[117]</sup>. This decellularized scaffold is transplanted orthotopically or ectopically. The decellularization of whole organ was first introduced by Ott *et al*<sup>[118]</sup> in 2008 with the aim of developing acellular hearts from mice. Bovine heart valves and corneas or those from pigs have already been commercialized and clinically applied<sup>[119]</sup>. In recent years, research has been conducted on human liver and hepatocytes. Mazza *et al*<sup>[2]</sup> reported in 2015 that human liver was decellularized and re-cellularized with a liver cell line to create engineered livers.

KaKabadze *et al*<sup>[15]</sup> engrafted sheep liver cells on decellularized human placenta and transplanted them into sheep that underwent partial hepatectomy. Human placenta was considered as an attractive source because it has a well-developed vascular network and ECM for tissue engineering. Moreover, it is usually discarded and widely available.

In addition, many articles exhibited the application of decellularized tissues and biomaterial-based scaffold.

As biomaterials, natural biomaterials are applied such as collagen and hyaluronic acid, and synthetic materials such as polymers based on polylactic acid and polyglycolic acid, among others<sup>[16-18]</sup>. Previous reports show that after transplanting these scaffolds, the liver function in recipients improved<sup>[19-21]</sup>.

More recently, bio-printed scaffolds have been developed that mimic the tissue using these biomaterials<sup>[120]</sup>. However, they have problems of vascularization for tissue engraftment and repopulation, which warrant further research.

Meanwhile, scaffold-based transplantation with an ECM was proven effective, and further research is underway with an aim to select ideal cells for humans<sup>[19]</sup>.

iPSCs and few other cell sources are seeded and cultured in decellularized tissue and other scaffolds such that tissue regeneration *in vitro* can be performed. Therefore,

**Table 3 Scaffold-based transplantation**

Donor			Recipients (strain)	Outcomes	Year	
Scaffold	Species	Seeding cell				
Decellularized organ liver	Human		Mouse (C57BL/6J)	Immunogenicity	2015 <sup>[2]</sup>	
			Rat (F344)	Immunogenicity	2013 <sup>[86]</sup>	
	Porcine		Porcine	Immunogenicity	2013 <sup>[87]</sup>	
			Porcine	Engraftment	2012 <sup>[88]</sup>	
	Sheep, rat		Sheep, rat	Engraftment	2015 <sup>[89]</sup>	
	Rat	Hepatocytes (rat), BM- MSCs (Rat)	Rat (Lewis)	Engraftment	2014 <sup>[90]</sup>	
			Hepatocytes (rat)	Rat (Lewis)	Engraftment, Hepatic function	2010 <sup>[91]</sup> , 2011 <sup>[92]</sup>
	Mouse		Hematopoietic progenitor cells (mouse)	Mouse (C57BL/6)	Hepatic function, metabolic function	2018 <sup>[93]</sup>
			BM-MSCs (mouse)	Mouse (NOD-SCID)	Survival extension, hepatic function	2014 <sup>[94]</sup>
	Placenta	Human	Liver cells (sheep)	Sheep	Survival extension, hepatic function	2018 <sup>[15]</sup>
Amniotic membrane	Human	AD-MSCs (human)	Mouse	Survival extension, hepatic function	2015 <sup>[95]</sup>	
Nonwoven polyglycolic acid scaffolds		Liver cells (human, mouse)	Mouse (NOD/SCID)	Analysis of human metabolite	2017 <sup>[19]</sup>	
3D hydrogel		Hepatocytes (human)	Mouse (nude)	Engraftment, hepatic function	2016 <sup>[16]</sup>	
Hyaluronan tube		Hepatocytes (rat), adipose-MSCs (human)	Rat (nude)	Engraftment, hepatic function	2016 <sup>[17]</sup>	
Polyethylene glycol hydrogels		Hepatocytes (rat)	Mouse (Nude)	Engraftment	2015 <sup>[20]</sup>	
Microbeads		Hepatocytes (rat)	Rat (SD)	Hepatic function	2014 <sup>[96]</sup>	
Poly-L-glycolic acid		Hepatocytes (mouse)	Mouse (NOD/SCID)	Engraftment	2014 <sup>[21]</sup>	
Hyaluronan hydrogels		Hepatic stem cells (human)	Mouse (Athymic nude)	Engraftment	2013 <sup>[97]</sup>	
Apatite-fiber scaffold		Hepatocytes (mouse) + HSC + SECs	Mouse (BALB/CA nu)	Hepatic function	2011 <sup>[98]</sup>	
Chitosan-alginate fibrous scaffolds		BM-MSCs (human)	Rat (Wistar)	Hepatic function	2010 <sup>[99]</sup>	
Hyaluronic acid sponge		Fetal hepatocyte (rat)	Rat (LEC)	Engraftment, hepatic function	2010 <sup>[18]</sup>	

3D: Three dimensional; SD: Sprague dawley; HSCs: Hematopoietic stem cells; BM-MSCs: Bone marrow derived mesenchymal stem cells.

further research should aim to solve this problem for actualizing its application clinically.

### **Conclusion and future perspectives**

Our study summarized alternative therapies for OLT. Alternative therapies have been deeply researched, particularly xeno-organ, scaffold-based, and cell transplantations. Clinically, only cell transplantation with hepatocytes or MSCs has been applied.

Scaffold-based transplantation is a comprehensive treatment that combines xeno-organ and cell transplantations. Future research on the clinical application of scaffold-based transplantation is expected.

**Table 4 Sources of alternative therapy**

Donors	Species	Numbers
Organ liver	Total	25
	Human	1 <sup>[2]</sup>
	Porcine	16 <sup>[5,14,74-84,86-88]</sup>
	Sheep	1 <sup>[89]</sup>
	Rabbit	1 <sup>[85]</sup>
	Rat	4 <sup>[89-92]</sup>
	Mouse	2 <sup>[93,94]</sup>
	Hepatocytes (adult)	Total
Hepatocytes (adult)	Human	10 <sup>[13,16,22-29]</sup>
	Rat	14 <sup>[17,20,30-37,90-92,96]</sup>
	Mouse	7 <sup>[21,38-42,98]</sup>
Hepatocytes (fetal)	Total	3
	Rat	2 <sup>[18,43]</sup>
	Mouse	1 <sup>[44]</sup>
Liver cells	Total	3
	Human	1 <sup>[19]</sup>
	Sheep	1 <sup>[15]</sup>
	Rabbit	1 <sup>[45]</sup>
MSCs (umbilical cord)	Human	3 <sup>[29,48,49]</sup>
MSCs (bone marrow)	Total	15
	Human	9 <sup>[50-52,54-58,99]</sup>
	Macaques	1 <sup>[59]</sup>
	Rabbit	1 <sup>[53]</sup>
	Rat	3 <sup>[60,61,90]</sup>
MSCs (Adipose)	Mouse	1 <sup>[94]</sup>
	Total	4
	Human	2 <sup>[17,63]</sup>
MSCs (liver)	Mouse	2 <sup>[64,65]</sup>
	Human	1 <sup>[62]</sup>
Hematopoietic stem cells	Human	2 <sup>[54,66]</sup>
ESCs	Mouse	1 <sup>[67]</sup>
iPSCs	Total	3
	Human	2 <sup>[68,69]</sup>
	Mouse	1 <sup>[70]</sup>
GPSCs	Mouse	1 <sup>[72]</sup>
Liver stem cells	Total	2
	Human	1 <sup>[97]</sup>
	Rat	1 <sup>[73]</sup>

MSCs: Mesenchymal stem cells; ESCs: Embryonic stem cells; iPSCs: Induced pluripotent stem cells; GPSCs: Germ line cell-derived pluripotent stem cells.

## ARTICLE HIGHLIGHTS

### **Research background**

Orthotopic liver transplantation (OLT) is the only treatment for end-stage liver failure; however, the shortage of donor organs limits its application. To overcome this problem, many researchers have attempted to develop alternatives to OLT.

### **Research motivation**

There are several reports of alternative therapies. Nevertheless, no study has comprehensively analyzed these therapies from varying perspectives.

### **Research objectives**

This systematic review aims to summarize the current status of alternative transplantation

therapies for OLT and to support future research.

### Research methods

A systematic review was performed by searching the PubMed, Cochrane Library and EMBASE databases for studies concerning alternative transplantation therapy for OLT. We used the following MeSH terms: “liver transplantation”, “cell”, “differentiation”, “organoid”, and “xenotransplantation”. Various types of studies were retrieved for full-text evaluation. Of these, we selected articles involving *in vivo* transplantation.

### Research results

A total of 89 studies were selected. There are three principle forms of treatment: Xeno-organ transplantation (14 articles), scaffold-based transplantation (22 articles), and cell transplantation (53 articles). Various types of sources for transplantation were discussed: Organ liver, 25 articles; adult hepatocytes, 31 articles; mesenchymal stem cells (MSCs), 25 articles; induced pluripotent stem cells, three articles and other sources. Clinical applications were discussed only for cell transplantation (12 studies; four studies using hepatocytes, five studies using umbilical cord-derived MSCs, three studies using bone marrow-derived MSCs, and two studies using hematopoietic stem cells).

### Research conclusions

This systematic review summarized alternative therapies for OLT from varying perspectives. Alternative therapies have been deeply researched, particularly xeno-organ, scaffold-based, and cell transplantation. Clinically, only cell transplantation with hepatocytes and MSCs have been applied. Scaffold-based transplantation is a comprehensive treatment that combines xeno-organ and cell transplantations. Future research on the clinical application of scaffold-based transplantation is expected.

### Research perspectives

This systematic review describes the current status of alternative therapy for OLT in end-stage liver failure. Further studies are needed for clinical applications in the future.

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