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Review Article

# Recent Application of Polycaprolactone Scaffolds and Its Composites for Tissue Engineering: a Review

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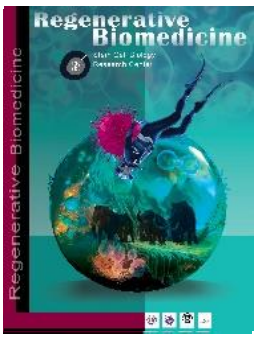
**ABSTRACT**

Polycaprolactone is a synthetic aliphatic polyester that has gained extensive attention in tissue engineering because of its excellent biodegradability, biocompatibility, and processability. Its mechanical strength, flexibility, and slow degradation rate make it a suitable candidate for constructing scaffolds with controllable porosity and architecture. This review highlights recent advancements in polycaprolactone-based nanofiber scaffolds and their composites for regenerating various tissues, including bone, cartilage and ligament, liver, cardiovascular, nerve, corneal, and skin. In bone and cartilage engineering, electrospun polycaprolactone fibers blended with ceramics or natural polymers such as collagen, chitosan, gelatin, or hydroxyapatite have enhanced osteoconductivity, chondrogenic differentiation, and mechanical stability. In hepatic and cardiac applications, polycaprolactone composites integrated with conductive polymers, extracellular matrix components, or nanoparticles have improved bioactivity, angiogenesis, and electrical conductivity. Furthermore, in neural and corneal tissue regeneration, aligned and surface-modified polycaprolactone nanofibers have promoted cell attachment, neurite extension, and corneal transparency. In skin tissue engineering, hybrid scaffolds incorporating bioactive agents such as aloe vera or curcumin demonstrated accelerated wound healing, fibroblast proliferation, and reduced inflammation. Despite the progress achieved, challenges remain regarding limited hydrophilicity, slow degradation rate, and the need for optimized cell–biomaterial interactions. Future research should focus on combining polycaprolactone with natural biopolymers and nanoscale modifications to develop biointeractive scaffolds with enhanced regenerative capacity. Overall, polycaprolactone and its composites represent a versatile and promising platform for the next generation of biomimetic scaffolds in regenerative medicine and tissue repair.

**Keywords:** Composite Biomaterials, Nanofibers, Polycaprolactone (PCL), Regenerative medicine, Tissue engineering



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## Introduction

Tissue engineering has revolutionized modern therapeutic approaches by enabling the repair and regeneration of damaged tissues and organs, thereby improving the quality of life for millions of patients worldwide(1). Among various strategies, the use of biodegradable polymeric scaffolds has attracted significant attention because these materials can provide a temporary three-dimensional structure for cell attachment, proliferation, and differentiation, ultimately supporting new tissue formation(2). Natural polymers have often been favored due to their inherent biodegradability, cytocompatibility, and excellent mechanical and biochemical properties; however, their purification and sterilization processes can be challenging, and they may occasionally induce immunogenic responses when used as allografts (1).

Polycaprolactone (PCL), a synthetic aliphatic polyester, was first synthesized by the Carothers group in the early 1930s and has since been widely used in biomedical applications (3,4). PCL is typically synthesized by ring-opening polymerization of ε-caprolactone using cationic, anionic, or radical initiators (5,6). It undergoes slow degradation through non-enzymatic hydrolysis, and its by-products are safely eliminated through the tricarboxylic acid cycle or renal excretion (7). Importantly, PCL is approved by the U.S. Food and Drug Administration (FDA) for certain clinical applications (8).

In tissue engineering, scaffolds must be biocompatible, biodegradable, and mechanically stable while supporting cell adhesion and proliferation (9,10). The structural features of a scaffold—such as porosity, architecture, degradation rate, and mechanical resistance play a vital role in its performance (11). Recent advances have led to the design of composite and nanofibrous PCL scaffolds that closely mimic the natural extracellular matrix, enhancing their functionality in biomedical applications including wound healing, vascular grafts, and drug delivery (12,13).

Therefore, this review aims to summarize the recent developments, applications, and challenges of PCL-based scaffolds and their composites in bone, ligament and cartilage, liver, cardiovascular, nerve, corneal, and skin tissue engineering.

## Applications

### Bone tissue engineering using PCL nanofibrous scaffold

Bone is an intricate construction consisting of collagen and nano-hydroxyapatite. Bone is important as a body shaper, provider of structural, mechanical resistance, the regulator of blood pH and calcium, phosphate for metabolic actions (14). In recent years, bone fracture and related disorders due to population growth, osteoporosis, and osteoarthritis, bone tumors, injuries caused by sports activities, and driving accidents have raised significant public health concerns (15). Bone tissue engineering remains a promising solution to overcome bone resorption (16). Previous studies have been demonstrated PCL with osteoconductive property, and thus mineralization can be an appropriate scaffold for bone regeneration (17,18).

Appropriate scaffolds for bone regeneration must have suitable structure, mechanical properties and can support cell adhesion, proliferation, and differentiation (19,20).


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Recently PCL and copolymers have been considered due to their appropriate mechanical properties and ability to regulate polymer degradation with bone regeneration (21). The method employed for constructing PCL scaffolds depends on the desired scaffold type. For fabricating fibrous scaffolds, techniques such as electrospinning and melt electrospinning are commonly applied. In contrast, methods including 3D bioprinting, solvent casting and porogen leaching, freeze-drying, $CO_2$ saturation and release, and phase separation are typically used to produce porous scaffolds (22,23). Electrospinning is one of the most common scaffolding methods in tissue engineering. The fibrous structure creates a vast surface area relative to the volume, which is desirable for cell attachment, proliferation, and stability (24,25). Electrospun PCL is widely used as a scaffold in bone regeneration due to easy spinning. In various studies, it has been merged with biopolymers, ceramics, and sometimes drugs to improve its physical and chemical properties (26,27). Sadeghian et al. fabricated a dual-drug-loaded PCL/chitosan bilayer scaffold containing dexamethasone and ascorbic acid to promote osteogenic differentiation. The sustained release of these bioactive agents for about two weeks significantly enhanced the proliferation and growth of human mesenchymal stem cells on the scaffold surface. Microscopic and biochemical analyses confirmed that the PCL/chitosan structure effectively supported cell attachment, proliferation, and osteogenic differentiation, indicating its strong potential for bone tissue engineering applications (28)

Electrospun PCL/octacalcium phosphate scaffold was used in another study for bone tissue engineering. According to this research, despite the reduction in the average diameter of the PCL fibers and octacalcium phosphate particles, the scaffold mechanical properties improved. Following the hydroxyapatite, phase formation was seen on the scaffold, and bone regeneration was also reported after implantation of human osteoblasts on this scaffold (29).

In another study, MG-63 osteoblast-like cells were seeded on PCL electrospun with bioactivate glass nanoparticles. Evaluations showed that this scaffold could support the MG-63 cells adhesion and proliferation (30).

In another study, a polycaprolactone/gelatin (PCL/GEL) nanofibrous scaffold reinforced with nano-hydroxyapatite and different concentrations of platelet-rich fibrin (PRF) was fabricated using electrospinning and freeze-drying methods. The scaffold containing a medium level of PRF exhibited the highest cell viability and enhanced osteogenic differentiation, as evidenced by increased expression of bone-related genes (COL1, RUNX2, and COLX) and improved cell morphology. These findings suggest that this scaffold composition can effectively support cell proliferation and bone tissue regeneration (31).

A composite scaffold composed of electrospun polycaprolactone (PCL) nanofibers and alginate hydrogel was developed to improve bone regeneration. The scaffold combined the mechanical strength and slow degradation of PCL with the biocompatibility of alginate, creating a favorable environment for cell growth. Results showed enhanced mechanical properties, slower degradation, and higher cell viability compared to pure alginate

hydrogel. Moreover, increased alkaline phosphatase activity and mineralization confirmed its osteogenic potential. Overall, the PCL–alginate scaffold demonstrated excellent biocompatibility and mechanical performance, making it a promising candidate for bone tissue engineering applications (32). In another study, an electrospun third-generation polycaprolactone (PCL) barrier membrane (BM) was developed by incorporating nano-hydroxyapatite (nHAP) and gentamicin (GEN) to enhance guided bone regeneration. The membrane exhibited high porosity and interconnectivity, supporting cell adhesion and proliferation while effectively preventing bacterial contamination. Structural and mechanical analyses confirmed the successful incorporation of nHAP and GEN, influencing fiber morphology and drug release. The membrane showed strong antibacterial activity against S. aureus, S. mutans, and P. aeruginosa, and nHAP addition improved cell viability and mineralization. Overall, the PCL/nHAP/GEN composite BM demonstrated excellent bioactivity, antibacterial performance, and biocompatibility, making it a promising candidate for guided bone regeneration applications(33).

**Ligament and cartilage tissue engineering using PCL nanofibrous scaffold**

Ligaments are fibrous connective tissues that connect bones and play a crucial role in maintaining joint stability and guiding movement. They transmit tensile loads, limit excessive motion, and preserve joint integrity. To regenerate ligaments with mechanical characteristics similar to native tissue, composite electrospun nanofibrous scaffolds incorporating chitosan (CS) and cellulose nanocrystals (CNCs) into the PCL matrix have been developed (34). These scaffolds exhibited a tensile strength of 39.3 MPa and an elastic modulus of 540.5 MPa, closely matching native ligament properties, and promoted tenocyte attachment and tenogenic differentiation. For anterior cruciate ligament (ACL) repair, dual-phase PCL/PLGA scaffolds with aligned fibers in the center and randomly oriented fibers at both ends were designed to mimic the zonal architecture of native ligaments. By tailoring the composition, a degradation rate compatible with tissue regeneration was achieved (35).

In contrast, cartilage functions to distribute mechanical loads and provide a low-friction surface. Recent studies indicate that the mechanical and biological properties of PCL-based scaffolds can be optimized through fabrication methods and material combinations. PCL–CS/MWCNT nanofibrous scaffolds integrated with chemically functionalized silk fabrics enhanced tensile strength, hydrophilicity, and chondrocyte adhesion and proliferation (36). The TIPS technique was used to fabricate porous PCL/collagen type I scaffolds, which improved cell viability and extracellular matrix (ECM) synthesis (37). Using multi-spray printing, PCL/alginate scaffolds composed of alternating layers of cells and matrix were fabricated; upon TGF-β stimulation, deposition of GAGs and type II collagen increased, leading to high-fidelity cartilage regeneration (38). Moreover, E-jet 3D printing enabled the production of PCL/polyvinylpyrrolidone (PVP) scaffolds with excellent stability and cell viability (39).


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3D-printed PCL/fibrin scaffolds functionalized with acellular solubilized ECM further enhanced porosity, water absorption, compressive strength, and ADSC chondrogenic differentiation (40).

Overall, PCL-based scaffolds hold great potential in ligament and cartilage tissue engineering due to their tunable mechanical and biological properties. For ligament regeneration, emphasis should be placed on tensile strength and fiber alignment, while for cartilage repair, focus should be on compressive resilience and zonal organization. Hybrid strategies combining electrospinning and 3D printing may integrate the advantages of both methods, providing multifunctional scaffolds capable of achieving both tensile and compressive performance.

## Liver tissue engineering using PCL nanofibrous scaffold

In the human body, the Liver is actively involved in the metabolism of various macromolecules such as carbohydrates, proteins, lipids, and vitamins (41). Also, it actively participates in the production of bile, enzyme activation, detoxification of exogenous and endogenous substances, xenobiotic biotransformation, and protein synthesis. Liver parenchymal cells, predominantly hepatocytes, are the main cellular component of the liver tissue with high capability (42).

The Liver non-parenchymal cells consist of the remaining cellular component and have a pivotal role in the hepatic structure and contribute to various functions, including supporting the hepatocyte activity (43). In spite of the high regenerative potential of hepatic tissue, damage to the Liver from acute or chronic injuries such as infection, nonalcoholic steatohepatitis, viral hepatitis, alcohol abuse, and autoimmune hepatitis is particularly devastating as a result of common scarring response from this organ. In the treatment of hepatic disorders, conventional methods, such as organ transplantation from an appropriate donor, have several problems, including immune response against transplanted tissue and donor tissue scarcity. During the past few decades, tissue engineering and regenerative medicine have shown great promise to mimic the architectural complexity and function of native hepatic tissue using various approaches. The synthesis of 3D scaffolds using the electrospinning technique has been introduced into the liver tissue engineering field by using various biomaterials, including PCL. The results of various studies indicated that PCL supported human stem cells, and the electrospinning method was the most commonly utilized technique for creating engineered hepatic tissue. Many promising studies using PCL nanofiber for hepatic tissue engineering have been reported due to slow degradability, biocompatibility, and suitable mechanical capabilities (44). Optimization of electrospun polycaprolactone (PCL) scaffolds demonstrated that both surface topography and biochemical composition significantly affect hepatocyte behavior. Scaffolds with small nanotopographies (~0.37 μm) enhanced HepG2 cell attachment, proliferation, and functional activity compared to larger microtopographies (2 μm).

Incorporation of decellularized rat and human liver extracellular matrix into topographically modified PCL fibers

maintained uniform morphology and promoted hepatocytes to form dense, monolayer-like structures with increased albumin gene expression. Hybrid scaffolds also supported steady growth and bioactivity of primary hepatocytes, with higher DNA content and fibronectin expression.

Overall, the study shows that combining nanoscale topographical cues with biochemical components can synergistically modulate hepatocyte physiology, offering a reproducible strategy for designing biomimetic scaffolds in liver tissue engineering and in vitro hepatic models (45).

Bual et al .developed electrospun nanofibrous scaffolds composed of liver-derived extracellular matrix (L-ECM), gelatin, and polycaprolactone (PCL) to enhance the biofunctionality of gelatin/PCL scaffolds. FTIR analysis confirmed the successful incorporation of L-ECM, while tensile strength and water contact angle tests demonstrated suitable mechanical properties and improved hydrophilicity.

Scanning electron microscopy revealed a uniform nanofibrous morphology, and in vitro culture of primary hepatocytes showed enhanced cell adhesion, proliferation, and formation of tissue-like structures on L-ECM–containing scaffolds. Moreover, hepatocytes exhibited higher liver-specific functions compared to those cultured on gelatin/PCL scaffolds.

These findings indicate that the electrospun L-ECM scaffolds developed by Ronald Bual et al. provide a biomimetic and biocompatible microenvironment suitable for liver tissue engineering and regeneration (46).

In a recent study, electrospun polycaprolactone (PCL) scaffolds with varying fibre morphologies were investigated to evaluate their impact on hepatocyte behavior. Both immortalised hepatic cell lines and mouse primary hepatocytes were cultured on scaffolds with large (4–5 μm) and small (1–2 μm) fibres in random, aligned, and highly porous cryogenically spun configurations. Analyses of cell attachment, proliferation, morphology, and expression of liver-specific proteins and genes revealed that scaffold morphology significantly affects hepatocyte structure and function. In particular, variations in fibre alignment and diameter modulated key hepatic markers such as CYP1A2, demonstrating that scaffold architecture plays a crucial role in maintaining and regulating hepatocyte functionality in vitro(47).

**Cardiovascular tissue engineering using PCL nanofibrous scaffold**

Cardiovascular tissue engineering is a branch of tissue engineering that aims to fabricate cell-free and cell-seeded vessels, heart valve, and cardiac tissue in order to find treatments for cardiovascular diseases. Due to spinnability and mechanical stability, PCL has frequently been used in this field. In a study on tissue-engineered heart valves, a biomimetic artificial valve scaffold was developed using a three-layer composite structure of polycaprolactone (PCL) and polyurethane (PU) fabricated through 3D printing and electrospinning. The scaffold consisted of an inner PCL layer, a middle PCL/PU (1:2) layer, and an outer PCL layer. Mechanical testing showed that this configuration achieved an elastic modulus of 14.7 MPa, closely matching that of natural heart valves, and exhibited strong circumferential mechanical properties. In vitro experiments confirmed excellent


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cytocompatibility, with a 99.8% cell survival rate after 14 days of culture. The multilayered architecture effectively mimics the native structure of mammalian heart valves, promoting cell proliferation and differentiation, and offers a promising strategy for developing functional tissue-engineered valves for interventional heart treatments (48). Polycaprolactone (PCL) has gained significant attention as a potential scaffold material in vascular tissue engineering due to its favorable properties. Current studies aim to further improve its mechanical strength, bioactivity, and surface hydrophilicity by employing various modification and composite approaches to make it more suitable for vascular regeneration. For example, electrospun PCL scaffolds functionalized with the angiogenic peptide KLTWQELYQLKYKGI (QK) have demonstrated improved endothelial cell adhesion and alignment, leading to enhanced vascular network formation (49). Double-porous polycaprolactone/chitosan (PCL/CS) composite scaffolds produced through phase separation have shown remarkable structural flexibility. By varying the ratio of components, scaffolds containing microvoids (20–90 μm) and micropores (7–20 μm) were obtained, which effectively supported the adhesion, spreading, and cytoskeletal organization of human umbilical vein endothelial cells—highlighting their potential for use in small-diameter vascular grafts. Furthermore, melt electrowriting, an advanced high-precision 3D printing technique, has been utilized to create PCL/polylactic acid (PLA) composite scaffolds with highly controlled microarchitectures, offering further opportunities for vascular tissue engineering applications (50,51). These PCL-based composite scaffolds displayed superior mechanical performance and improved surface hydrophilicity, leading to stronger interactions with endothelial cells. Such properties underline their potential as promising candidates for cardiovascular tissue repair and regeneration.

## Nerve tissue engineering using PCL nanofibrous scaffold

Scaffolds designed for neural tissue engineering need to exhibit both mechanical softness and electrical conductivity to match the biomechanical and electrophysiological characteristics of nervous tissue (52–56). Incorporating microchannels or guidance structures within these scaffolds is also crucial for directing axonal regeneration. Electrospun scaffolds have shown significant promise in this field because of their fibrous flexibility and capacity to integrate functional components. For instance, electrospun PCL/chitosan/polypyrrole (PCL/CS/PPy) composite nanofibers have shown improved hydrophilicity and electrical conductivity, which in turn enhanced PC12 cell adhesion, proliferation, and neurite extension—demonstrating their potential to facilitate neuronal repair and regeneration (57). Incorporating gelatin (Gel) into PCL nanofibers further enhanced the scaffold's bioactivity and refined its microstructural characteristics. This modification promoted improved neurogenic differentiation and facilitated greater neurite outgrowth of PC12 cells, indicating the scaffold's increased potential for neural tissue regeneration(58).

Taraf et al. Fabricated PCL nanofiber scaffolds by electrospinning and differentiated endometrial stem cells (EnSC)

into neuron-like cells on them. They used these scaffolds to repair hemisected spinal cord injury in rats. They used crocin to reduce inflammation at the site of the lesion and prevent nerve cell death in the secondary phase of the injury (59).

Babaloo et al. with co-culture of endometrial stem cells (EnSC) and Schwann cells on an inserted well and seeded these cells on PCL/gelatin nanofiber scaffolds differentiated EnSC into neuron-like cells and used these scaffolds to repair spinal cord injury in a model of hemisected rats and these scaffolds proposed using for central nerve tissue engineering application (60). Kheradmand et al. in 2020 Using PCL / gelatin nanofiber scaffolds and Differentiated CGR8 embryonic stem cells into dopaminergic cells using the synergistic effect of beta-boswellic acid (BBA) and developed a new method for treating Parkinson's disease(6).

In another study developed an integrated therapeutic platform combining electrospun polycaprolactone/functionalized multi-walled carbon nanotube (PCL/f-MWCNT) scaffolds, liposomal ellagic acid (EA@lip), and adipose-derived mesenchymal stem cells (ADMSCs) for spinal cord injury (SCI) repair. The PCL/f-MWCNT scaffolds exhibited well-aligned nanofibers, and EA@lip coating significantly improved hydrophilicity and biocompatibility. In vitro analyses confirmed that ADMSCs adhered, proliferated, and survived effectively on the liposome-coated scaffolds, while oxidative stress assays demonstrated strong antioxidant and anti-inflammatory effects. In vivo evaluation using a rat dorsal hemisection model showed that the hybrid scaffold promoted myelin and neuronal regeneration, improved motor function, and restored oxidative balance. Gene expression analysis revealed downregulation of COX2 and upregulation of GPX1, MBP, and Slc17a6/7, indicating reduced inflammation and enhanced neuroprotection. Overall, the combination of EA@lip-coated PCL/f-MWCNT scaffolds with ADMSCs presents a promising strategy for promoting structural and functional recovery following spinal cord injury (55).

**Corneal tissue engineering using PCL nanofibrous scaffold**

Millions of patients around the world annoy from corneal defects due to infection, trauma, cancer, chemical injury, and pathological disorders of contiguous tissues (61). Although transplantation of allogeneic corneal is used in most countries, challenges such as the recipient's immune response, the lack of corneal donors, and the declining quality of the cornea due to LASIK surgery have prompted scientists to consider replacing it with tissue engineering (62). In recent years, the design of biocompatible and degradable scaffolds for corneal tissue engineering and the selection of suitable cells for the regeneration of corneal layers, including epithelial, stromal, and endothelial, have been extensively studied (63).

Baradaran-Rafii and colleagues developed an electrospun polycaprolactone (PCL) nanofibrous scaffold designed to support the expansion of limbal stem cells (LSCs) as a potential substitute for ocular epithelial regeneration. Biocompatibility and viability assessments demonstrated excellent cell attachment and proliferation on the scaffold surface, confirming its strong biocompatibility and ability to preserve the normal phenotype of corneal stem cells.


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Furthermore, the PCL substrate facilitated the formation of a three-dimensional corneal epithelium with an expression profile comparable to that of the human amniotic membrane (AM). These findings indicate that electrospun PCL scaffolds represent a promising alternative substrate for limbal stem cell transplantation and corneal tissue regeneration (64).

Sharma and colleagues developed an electrospun polycaprolactone (PCL) scaffold as a limbal stem cell substrate, proposing it as a potential alternative to the human amniotic membrane (HAM) for ocular surface reconstruction. Biocompatibility assessments revealed excellent cell adhesion and proliferation, as human corneal epithelial (HCE-T) cells formed a continuous, well-attached epithelial layer while maintaining a normal corneal phenotype. These findings demonstrated that electrospun nanofibers provide a favorable microenvironment for limbal epithelial cell (LEC) expansion and can serve as an effective carrier for ocular surface tissue engineering. Furthermore, plasma surface modification was explored to enhance corneal cell interaction, showing comparable proliferation and gene expression profiles to HAM controls. Overall, the PCL electrospun scaffold exhibited the desired biocompatibility and functionality, making it a promising candidate for corneal tissue regeneration and transplantation (65,66).

In another study, Sanie-Jahromi and colleagues evaluated electrospun scaffolds composed of polycaprolactone (PCL) and gelatin for culturing limbal epithelial stem cells (LESCs). The cellular assessments revealed that LESCs cultured on PCL scaffolds exhibited superior morphology and proliferation compared to those on PCL/Gel composites. Histopathological examination of corneal tissues from transplanted animals confirmed successful epithelial regeneration in both scaffold groups; however, the PCL-only group showed markedly reduced vascularization and inflammation. These findings suggest that pure PCL electrospun scaffolds provide a more favorable environment for corneal surface reconstruction by minimizing inflammatory responses while supporting epithelial regeneration(66).

In another study, Carter and colleagues cultured mesenchymal stem cells (MSCs) on both two-dimensional and three-dimensional PCL/gelatin scaffolds to evaluate their wound-healing potential. The findings demonstrated that MSC-seeded scaffolds significantly enhanced epithelialization and accelerated wound closure compared to untreated controls. These results indicated that MSCs effectively promote tissue regeneration and improve the biological performance of PCL/gelatin nanofiber scaffolds, highlighting their promise for wound healing applications (67).

## Skin tissue engineering using PCL nanofibrous scaffold

In the field of tissue engineering, polycaprolactone (PCL)-based scaffolds are extensively utilized for skin wound healing due to their favorable mechanical properties, including softness, flexibility, and resilience. Techniques such as electrospinning and freeze-drying are frequently employed to fabricate these scaffolds. However, the inherent hydrophobicity of PCL restricts efficient cell adhesion and tissue regeneration. To overcome this drawback,

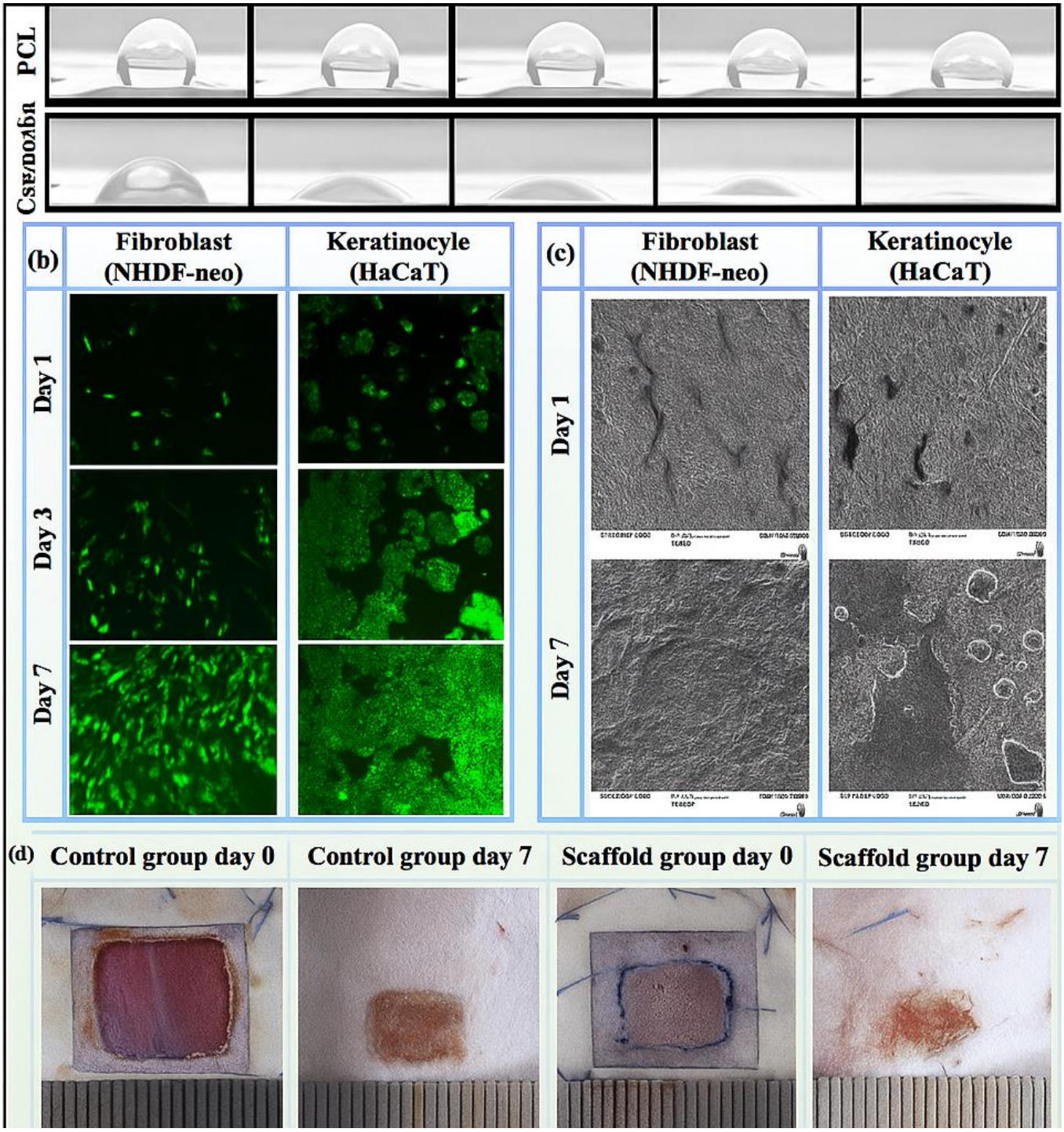


**Figure 1. (a–d)** illustrates the characterization and biological performance of PCL/collagen/chitooligosaccharide (COS) composite scaffolds with a fish collagen to PCL ratio of 9:1. Panel **(a)** shows the water contact angle (WCA) images demonstrating enhanced hydrophilicity of the composite compared to pure PCL. Panels **(b)** and **(c)** present fluorescence micrographs and SEM images, respectively, depicting the adhesion, spreading, and proliferation of NHDF-neo and HaCaT cells on the scaffold surface. Panel **(d)** highlights the in vivo wound-healing performance of the composite scaffold compared with the control group (Tegaderm-covered) seven days post-surgery, showing significantly accelerated re-epithelialization and tissue repair. *(Reproduced with permission from (70), Copyright 2021, Elsevier.)*


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researchers have incorporated natural polymers into PCL matrices to enhance both structural integrity and bioactivity. Blending PCL with materials such as cellulose, chitosan (CS), gelatin (Gel), silk fibroin (SF), or collagen has been shown to increase hydrophilicity, improve biocompatibility, and promote cellular attachment and proliferation (68,69)

For instance, Chandika et al. (70) fabricated electrospun PCL/fish collagen scaffolds functionalized with chitooligosaccharides (COS), which exhibited enhanced hydrophilicity and significantly accelerated wound healing in vivo by promoting re-epithelialization and dermal tissue remodeling (Fig.1). Additionally, the incorporation of cellulose nanocrystals (CNCs) and graphene oxide (GO) has been reported to further improve the mechanical strength and electrical conductivity of PCL-based scaffolds, creating a more biomimetic microenvironment that supports cell adhesion, proliferation, and migration (71,72).

Plant-derived bioactive compounds have further enhanced the functionality of PCL-based scaffolds for skin tissue engineering. The incorporation of peppermint essential oil (PEP) has imparted intrinsic antibacterial properties, providing an antibiotic-free approach for wound dressing applications (73). Additionally, composite scaffolds combining PCL with zein and gum Arabic (GA) have been engineered to better replicate extracellular matrix (ECM) architecture while improving mechanical strength and biocompatibility (74,75). Baghersad et al. (76) incorporated Aloe vera (AV) and tetracycline hydrochloride (TCH) into electrospun PCL/gelatin scaffolds, confirming AV integration through FTIR peaks corresponding to glycosidic bonds (1050–1090 $cm^{-1}$). These scaffolds exhibited excellent hydrophilicity (WCA < 40°) and supported high fibroblast viability (81% after 72 h). In vivo experiments demonstrated significantly accelerated wound closure relative to controls. Overall, both in vitro and in vivo findings highlight the potential of multifunctional PCL-based composites to promote epidermal regeneration, angiogenesis, and anti-inflammatory responses. Owing to their nanofibrous architecture, electrospun scaffolds are particularly advantageous for superficial wound healing, as they effectively facilitate cell attachment, proliferation, migration, haemostasis, and infection prevention.

Incorporation of synthetic polymers such as poly(L-lactide) (PLLA) and polyethylene glycol (PEG) (77), along with natural biopolymers like zein, chitosan (CS), and gelatin (Gel) (78,79), or therapeutic agents (80), into PCL matrices has enabled the fabrication of highly porous, structurally uniform, and interconnected scaffolds through freeze-drying techniques. These composite systems demonstrate enhanced hydrophilicity, antibacterial properties, and overall biological performance. For instance, Hakim et al. (81) fabricated PCL scaffolds blended with extra virgin olive oil (EVOO) and reported an inverse correlation between pore size and EVOO content (0–7 wt%), while maintaining non-cytotoxicity and strong antibacterial activity supportive of cell proliferation. Similarly, Jing et al. (82) In another study, a multi-gradient electrospun nanofibrous scaffold composed of

MgO/$MgCO_3$/polycaprolactone (PCL) was developed for peripheral nerve regeneration. By precisely adjusting the ratio of fast-degrading MgO to slow-degrading $MgCO_3$ and controlling the number of electrospun layers, the scaffold achieved a sustained release of $Mg^{2+}$ ions for up to six weeks. The controlled magnesium release effectively enhanced Schwann cell proliferation, migration, and transition to a repair-supportive phenotype. Transcriptomic analysis revealed that $Mg^{2+}$ modulated Schwann cell behavior primarily through activation of the Wnt signaling pathway. In a rat model with a 10 mm critical-sized sciatic nerve defect, implantation of the MgO/$MgCO_3$/PCL multi-gradient scaffold combined with a 3D-engineered PCL nerve conduit significantly improved axonal regeneration, remyelination, and muscle reinnervation after 12 weeks. Overall, this study introduced an innovative PCL-based scaffold capable of controlled magnesium release, elucidating the molecular mechanisms of magnesium-based biomaterials in neural repair and providing a strong theoretical foundation for future clinical translation (83).

## Conclusion

Polycaprolactone (PCL) and its composites have demonstrated remarkable versatility and potential across a wide spectrum of tissue engineering applications, including bone, cartilage, ligament, liver, cardiovascular, neural, corneal, and skin regeneration. Due to its outstanding biocompatibility, mechanical stability, and processability, PCL provides an ideal framework for supporting cell adhesion, proliferation, and differentiation. However, its inherent hydrophobicity, limited bioactivity, and slow degradation remain major obstacles to clinical translation.

Combining PCL with natural polymers such as gelatin, collagen, chitosan, and silk fibroin, as well as inorganic or conductive additives like hydroxyapatite, metal oxides, carbon nanotubes, and graphene, has significantly improved mechanical integrity, biological interactions, and tissue-specific regeneration.

Overall, the reviewed evidence suggests that the structural tunability and composite adaptability of PCL make it one of the most promising biomaterials for next-generation regenerative scaffolds capable of mimicking native extracellular matrix characteristics and promoting functional tissue restoration.

### Perspectives

Future research on PCL-based scaffolds should focus on bridging the gap between experimental success and clinical translation. A key direction involves designing multifunctional hybrid scaffolds that integrate biological, mechanical, and electrical cues to better replicate the dynamic in vivo microenvironment. Development of stimuli-responsive systems capable of reacting to biochemical or mechanical signals could enable controlled drug delivery and adaptive regeneration. Advances in surface modification, nanotechnology, and biofunctionalization are expected to enhance cell–material interactions and accelerate tissue remodeling. Moreover, adopting eco-friendly fabrication methods and scalable production processes will be essential for sustainable and cost-effective clinical application. Finally, the establishment of standardized evaluation protocols for


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biodegradation, biocompatibility, and mechanical performance, coupled with close collaboration between materials scientists, biomedical engineers, and clinicians, will play a decisive role in translating PCL-based technologies from laboratory research to therapeutic reality.

## References

1. Homaeigohar S, Boccaccini AR. Nature-Derived and Synthetic Additives to poly(ε-Caprolactone) Nanofibrous Systems for Biomedicine; an Updated Overview. Front Chem. 2022 Jan 19;9:809676.

2. Gharibshahian M, Salehi M, Beheshtizadeh N, Kamalabadi-Farahani M, Atashi A, Nourbakhsh MS, et al. Recent advances on 3D-printed PCL-based composite scaffolds for bone tissue engineering. Front Bioeng Biotechnol. 2023 Jun 19;11:1168504.

3. Woodruff MA, Hutmacher DW. The return of a forgotten polymer—Polycaprolactone in the 21st century. Prog Polym Sci [Internet]. 2010 Oct 1 [cited 2025 Nov 4];35(10):1217–56.

4. Massumi M, Abasi M, Babaloo H, Terraf P, Safi M, Saeed M, et al. The effect of topography on differentiation fates of matrigel-coated mouse embryonic stem cells cultured on PLGA nanofibrous scaffolds. Tissue Eng Part A. 2012 Mar 1;18(5–6):609–20.

5. Shah SR, Modi CD, Singh S, Mori DD, Soniwala MM, Prajapati BG. Recent Advances in Additive Manufacturing of Polycaprolactone-Based Scaffolds for Tissue Engineering Applications: A Comprehensive Review. Regenerative Engineering and Translational Medicine 2024 11:1 [Internet]. 2024 Sep 18 [cited 2025 Nov 4];11(1):112–31.

6. Kheradmand H, Babaloo H, Vojgani Y, Mirzakhanlouei S, Bayat N. PCL/gelatin scaffolds and beta-boswellic acid synergistically increase the efficiency of CGR8 stem cells differentiation into dopaminergic neuron: A new paradigm of Parkinson's disease cell therapy. J Biomed Mater Res A. 2021 Apr 1;109(4):562–71.

7. Liang HY, Lee WK, Hsu JT, Shih JY, Ma TL, Vo TTT, et al. Polycaprolactone in Bone Tissue Engineering: A Comprehensive Review of Innovations in Scaffold Fabrication and Surface Modifications. Journal of Functional Biomaterials 2024, Vol 15, [Internet]. 2024 Aug 24 [cited 2025 Nov 4];15(9).

8. Gharibshahian M, Salehi M, Beheshtizadeh N, Kamalabadi-Farahani M, Atashi A, Nourbakhsh MS, et al. Recent advances on 3D-printed PCL-based composite scaffolds for bone tissue engineering. Front Bioeng Biotechnol. 2023 Jun 19;11:1168504.

9. Murugan S, Parcha SR. Fabrication techniques involved in developing the composite scaffolds PCL/HA nanoparticles for bone tissue engineering applications. Journal of Materials Science: Materials in Medicine 2021 32:8 [Internet]. 2021 Aug 11 [cited 2025 Nov 4];32(8):1–10.

10. Robles KN, Zahra F tuz, Mu R, Giorgio T, Robles KN, Zahra F tuz, et al. Advances in Electrospun Poly(ε-caprolactone)-Based Nanofibrous Scaffolds for Tissue Engineering. Polymers 2024, Vol 16, [Internet]. 2024 Oct 10 [cited 2025 Nov 4];16(20).

11. Azari A, Golchin A, Maymand MM, Mansouri F, Ardeshirylajimi A. Electrospun Polycaprolactone Nanofibers: Current Research and Applications in Biomedical Application. Adv Pharm Bull [Internet]. 2021 [cited 2025 Nov 4];12(4):658.

12. Coppola B, Menotti F, Longo F, Banche G, Mandras N, Palmero P, et al. New Generation of Osteoinductive and Antimicrobial Polycaprolactone-Based Scaffolds in Bone Tissue Engineering: A Review. Polymers 2024, Vol 16, [Internet]. 2024 Jun 12 [cited 2025 Nov 4];16(12).

13. Raoufinia R, Hashemi S, Arabi K, Naghipoor K, Fakoor F, Saburi E. Poly ε-Caprolactone Scaffolds: Advancements in Bone Regeneration and Grafting. OBM Transplantation 2025, Vol 9, 245 [Internet]. 2025 Apr 2 [cited 2025 Nov 4];9(2):1–8.

14. Hassani A, Khoshfetrat AB, Rahbarghazi R, Sakai S. Collagen and nano-hydroxyapatite interactions in alginate-based microcapsule provide an appropriate osteogenic microenvironment for modular bone tissue formation. Carbohydr Polym [Internet]. 2022 Feb 1 [cited 2025 Nov 4];277:118807.

15. Aykora D, Uzun M. Bone tissue engineering for osteointegration: Where are we now? Polymer Bulletin

2024 81:10 [Internet]. 2024 Feb 3 [cited 2025 Nov 4];81(10):8595–605.

16. Asl RSR, Rahimzadeh-Bajgiran F, Saburi E. Evaluation of osteoconductive effect of polycaprolactone (PCL) scaffold treated with fibronectin on adipose-derived mesenchymal stem cells (AD-MSCs). Am J Stem Cells [Internet]. 2024 [cited 2025 Nov 4];13(3):152.

17. Gómez-Cerezo N, Casarrubios L, Saiz-Pardo M, Ortega L, de Pablo D, Díaz-Güemes I, et al. Mesoporous bioactive glass/ε-polycaprolactone scaffolds promote bone regeneration in osteoporotic sheep. Acta Biomater [Internet]. 2019 May 1 [cited 2025 Nov 4];90:393–402.

18. Jaber M, Poh PSP, Duda GN, Checa S. PCL strut-like scaffolds appear superior to gyroid in terms of bone regeneration within a long bone large defect: An in silico study. Front Bioeng Biotechnol. 2022 Sep 23;10:995266.

19. Ebrahimi Z, Irani S, Ardeshirylajimi A, Seyedjafari E. Enhanced osteogenic differentiation of stem cells by 3D printed PCL scaffolds coated with collagen and hydroxyapatite. Scientific Reports 2022 12:1 [Internet]. 2022 Jul 20 [cited 2025 Nov 4];12(1):1–15.

20. Ramírez-Ruiz F, Núñez-Tapia I, Piña-Barba MC, Alvarez-Pérez MA, Guarino V, Serrano-Bello J, et al. Polycaprolactone for Hard Tissue Regeneration: Scaffold Design and In Vivo Implications. Bioengineering 2025, Vol 12, [Internet]. 2025 Jan 8 [cited 2025 Nov 4];12(1).

21. Liu YY, Blázquez JPF, Yin GZ, Wang DY, Llorca J, Echeverry-Rendón M. A strategy to tailor the mechanical and degradation properties of PCL-PEG-PCL based copolymers for biomedical application. 2023 Aug 29 [cited 2025 Nov 4];

22. Smith JA, Mele E. Electrospinning and Additive Manufacturing: Adding Three-Dimensionality to Electrospun Scaffolds for Tissue Engineering. Front Bioeng Biotechnol. 2021 Nov 30;9:674738.

23. Robles KN, Zahra F tuz, Mu R, Giorgio T, Robles KN, Zahra F tuz, et al. Advances in Electrospun Poly(ε-caprolactone)-Based Nanofibrous Scaffolds for Tissue Engineering. Polymers 2024, Vol 16, [Internet]. 2024 Oct 10 [cited 2025 Nov 4];16(20).

24. Zamani M, Shakhssalim N, Ramakrishna S, Naji M. Electrospinning: Application and Prospects for Urologic Tissue Engineering. Front Bioeng Biotechnol. 2020 Oct 7;8:579925.

25. Zulkifli MZA, Nordin D, Shaari N, Kamarudin SK. Overview of Electrospinning for Tissue Engineering Applications. Polymers (Basel) [Internet]. 2023 Jun 1 [cited 2025 Nov 4];15(11):2418.

26. Elkhouly H, Mamdouh W, El-Korashy DI. Electrospun nano-fibrous bilayer scaffold prepared from polycaprolactone/gelatin and bioactive glass for bone tissue engineering. Journal of Materials Science: Materials in Medicine 2021 32:9 [Internet]. 2021 Aug 28 [cited 2025 Nov 4];32(9):1–15.

27. Qian C, Liu Y, Chen S, Zhang C, Chen X, Liu Y, et al. Electrospun core–sheath PCL nanofibers loaded with nHA and simvastatin and their potential bone regeneration applications. Front Bioeng Biotechnol. 2023 Jul 26;11:1205252.

28. Seddighian A, Ganji F, Baghaban-Eslaminejad M, Bagheri F. Electrospun PCL scaffold modified with chitosan nanoparticles for enhanced bone regeneration. Prog Biomater [Internet]. 2021 Mar 1 [cited 2025 Nov 4];10(1):65.

29. Heydari Z, Mohebbi-Kalhori D, Afarani MS. Engineered electrospun polycaprolactone (PCL)/octacalcium phosphate (OCP) scaffold for bone tissue engineering. Materials Science and Engineering: C [Internet]. 2017 Dec 1 [cited 2025 Nov 5];81:127–32.

30. Pitaluga LH, Souza MT, Zanotto ED, Romero MES, Hatton P V. Electrospun F18 Bioactive Glass/PCL—Poly (ε-caprolactone)—Membrane for Guided Tissue Regeneration. Materials [Internet]. 2018 Mar 8 [cited 2025 Nov 5];11(3):400.

31. Pestehei K, Ghiasi M, Moradkhani S, Fazel B, Ebrahimi S, Ghiasi A. Bioengineered hybrid electrospun scaffold of Polycaprolacton/Gelatin-nano-hydroxyapatite, coated with platelet-rich fibrin, for enhanced osteogenesis and bone healing using adipose derived stem cells. 2025 Sep 3 [cited 2025 Nov 5];

32. Ashrafi F, Emami A, Navaei-Nigjeh M, Izadi E, Salehi S, seyhoun I, et al. Regeneration of Bone Tissue Using Nanofibers Made from Electrospun Polycaprolactone (PCL) and a Hydrogel Composed of Alginate (Alg/PCL). Regenerative Engineering and Translational Medicine


https://doi.org/10.22034/jrb.2025.12.V1I4A4

2025 11:3 [Internet]. 2025 Mar 3 [cited 2025 Nov 5];11(3):750–9.

33. Mirica IC, Furtos G, Fontaine V, Vlassa M, Pascuta P, Petean I, et al. Electrospun Polycaprolactone Membranes Loaded with Gentamicin and Nano-Hidroxyapatite for Guided Bone Regeneration. Biomedicines [Internet]. 2025 Sep 25 [cited 2025 Nov 5];13(10):2349.

34. Domingues RMA, Chiera S, Gershovich P, Motta A, Reis RL, Gomes ME. Enhancing the Biomechanical Performance of Anisotropic Nanofibrous Scaffolds in Tendon Tissue Engineering: Reinforcement with Cellulose Nanocrystals. Adv Healthc Mater [Internet]. 2016 Jun 8 [cited 2025 Nov 6];5(11):1364–75. Available from: /doi/pdf/10.1002/adhm.201501048

35. Tang Y, Tian J, Li L, Huang L, Shen Q, Guo S, et al. Biomimetic Biphasic Electrospun Scaffold for Anterior Cruciate Ligament Tissue Engineering. Tissue Engineering and Regenerative Medicine 2021 18:5 [Internet]. 2021 Aug 5 [cited 2025 Nov 6];18(5):819–30.

36. Mirmusavi M, Karbasi S, ... MAIJ of, 2024 undefined. Chemofunctionalization of knitted silk to improve interface connection in a nano/micro scaffold based on polycaprolactone-chitosan-multi-walled carbon nanotube/silk. ElsevierMH Mirmusavi, S Karbasi, M Ahmadian, P Zadehnajar, F HeidariInternational Journal of Biological Macromolecules, 2024•Elsevier [Internet]. [cited 2025 Nov 6];

37. Munir N, Materials ACB, 2018 undefined. Novel phase separated polycaprolactone/collagen scaffolds for cartilage tissue engineering. iopscience.iop.orgN Munir, A CallananBiomedical Materials, 2018•iopscience.iop.org [Internet]. [cited 2025 Nov 6];

38. Kundu J, Shim JH, Jang J, Kim SW, Cho DW. An additive manufacturing-based PCL–alginate–chondrocyte bioprinted scaffold for cartilage tissue engineering. Wiley Online LibraryJ Kundu, JH Shim, J Jang, SW Kim, DW ChoJournal of tissue engineering and regenerative medicine, 2015•Wiley Online Library [Internet]. 2015 Nov 1 [cited 2025 Nov 6];9(11):1286–97.

39. Li K, Wang D, Zhao K, Song K, Talanta JL, 2020 undefined. Electrohydrodynamic jet 3D printing of PCL/PVP composite scaffold for cell culture. ElsevierK Li, D Wang, K Zhao, K Song, J LiangTalanta, 2020•Elsevier [Internet]. [cited 2025 Nov 6]

40. Honarvar A, Setayeshmehr M, Ghaedamini S, Hashemibeni B, Moroni L, Karbasi S. Chondrogenesis of mesenchymal stromal cells on the 3D printed polycaprolactone/fibrin/decellular cartilage matrix hybrid scaffolds in the presence of piascledine. Taylor & FrancisA Honarvar, M Setayeshmehr, S Ghaedamini, B Hashemibeni, L Moroni, S KarbasiJournal of Biomaterials science, Polymer edition, 2024•Taylor & Francis [Internet]. 2024 [cited 2025 Nov 6];35(6):799–822.

41. Flam E, Haas JT, Staels B. Liver metabolism in human MASLD: A review of recent advancements using human tissue metabolomics. Atherosclerosis [Internet]. 2025 Jan 1 [cited 2025 Nov 8];400.

42. Fleishman JS, Kumar S. Bile acid metabolism and signaling in health and disease: molecular mechanisms and therapeutic targets. Signal Transduction and Targeted Therapy 2024 9:1 [Internet]. 2024 Apr 26 [cited 2025 Nov 8];9(1):1–51.

43. Mata-Martínez E, Ramírez-Ledesma MG, Vázquez-Victorio G, Hernández-Muñoz R, Díaz-Muñoz M, Vázquez-Cuevas FG, et al. Purinergic Signaling in Non-Parenchymal Liver Cells. International Journal of Molecular Sciences 2024, Vol 25, [Internet]. 2024 Aug 30 [cited 2025 Nov 8];25(17).

44. Weber J, Linti C, Lörch C, Weber M, Andt M, Schlensak C, et al. Combination of melt-electrospun poly-ε-caprolactone scaffolds and hepatocyte-like cells from footprint-free hiPSCs to create 3D biohybrid constructs for liver tissue engineering. Scientific Reports 2023 13:1 [Internet]. 2023 Dec 13 [cited 2025 Nov 8];13(1):1–18.

45. Gao Y, Callanan A. Influence of surface topography on PCL electrospun scaffolds for liver tissue engineering. J Mater Chem B. 2021 Oct 14;9(38):8081–93.

46. Bual R, Kimura H, Ikegami Y, Shirakigawa N, Ijima H. Fabrication of liver-derived extracellular matrix nanofibers and functional evaluation in in vitro culture using primary hepatocytes. Materialia (Oxf) [Internet]. 2018 Dec 1 [cited 2025 Nov 8];4:518–28.

47. Bate TSR, Gadd VL, Forbes SJ, Callanan A. Response differences of HepG2 and Primary Mouse Hepatocytes to morphological changes in electrospun PCL scaffolds.

Scientific Reports 2021 11:1 [Internet]. 2021 Feb 4 [cited 2025 Nov 8];11(1):1–13.

48. Gao X, Liu Z, Zhang Z, Gao Y, Zhang J, Long Y, et al. Artificial Heart Valve Scaffold Based on Electrospun PCL/PU Three-Layer Composite Fibers. Applied Sciences 2024, Vol 14, [Internet]. 2024 Dec 21 [cited 2025 Nov 8];14(24).

49. Yaralı Çevik ZB, Sunal G, Taşkara A, Karaman O. Development of VEGF mimetic QK peptide on polycaprolactone nanofiber for vascular tissue engineering. Mater Today Commun [Internet]. 2024 Jun 1 [cited 2025 Nov 8];39:109026.

50. Das P, Remigy JC, Lahitte JF, van der Meer AD, Garmy-Susini B, Coetsier C, et al. Development of double porous poly (ε - caprolactone)/chitosan polymer as tissue engineering scaffold. Materials Science and Engineering: C [Internet]. 2020 Feb 1 [cited 2025 Nov 8];107:110257.

51. Shahverdi M, Seifi S, Akbari A, reports KMS, 2022 undefined. Melt electrowriting of PLA, PCL, and composite PLA/PCL scaffolds for tissue engineering application. nature.comM Shahverdi, S Seifi, A Akbari, K Mohammadi, A Shamloo, MR MovahhedyScientific reports, 2022•nature.com [Internet]. [cited 2025 Nov 8]

52. Abroumand Gholami A, Rahmani S, Moharreri P, Amirazodi E, Molavi AM, Mokhtari T, et al. Liposomal ellagic acid enhances the regenerative potential of ADMSC-laden nanofibrous PCL scaffolds in a rat model of spinal cord injury. Sci Rep [Internet]. 2025 Dec 1 [cited 2025 Oct 27];15(1):1–14.

53. Babaloo H, Barati S, Haghir H, Gholami AA, Moharreri P, Fallahnezhad S, et al. The effect of PU/MWCNT nanofiber scaffolds containing hesperidin nanoparticles and mesenchymal stem cells on the microglia and astrocyte phenotype in the spinal cord injury model. Neuroscience [Internet]. 2025 Sep 13 [cited 2025 Oct 28];583:53–62.

54. Moharreri P, Molavi AM, Abroumand Gholami A, Rahmani S, Mokhtari T, Gheybi F, et al. In vitro evaluation of bioactive PCL/alginate fibers with controlled liposomal silymarin release for mesenchymal stem cell transplantation. Sci Rep [Internet]. 2025 Dec 1 [cited 2025 Oct 28];15(1):35738.

55. Abroumand Gholami A, Rahmani S, Moharreri P, Amirazodi E, Molavi AM, Mokhtari T, et al. Liposomal ellagic acid enhances the regenerative potential of ADMSC-laden nanofibrous PCL scaffolds in a rat model of spinal cord injury. Scientific Reports 2025 15:1 [Internet]. 2025 Aug 18 [cited 2025 Nov 8];15(1):1–14.

56. Karami A, Molavi AM, Babaloo H, Farhadian N. Spinal Cord Injury Treatment by Applying a Composite Scaffold Transplanted with Mesenchymal Stem Cells and Chitosan-Coated Nanostructured Lipid Carriers of Curcumin. ACS Appl Bio Mater [Internet]. 2025 Aug 18 [cited 2025 Oct 27];8(8):6881–96.

57. Sadeghi A, Moztarzadeh F, Aghazadeh Mohandesi J. Investigating the effect of chitosan on hydrophilicity and bioactivity of conductive electrospun composite scaffold for neural tissue engineering. ElsevierA Sadeghi, F Moztarzadeh, JA MohandesiInternational journal of biological macromolecules, 2019•Elsevier [Internet]. 2019 Jan 1 [cited 2025 Nov 8];121:625–32.

58. Alvarez-Perez MA, Guarino V, Cirillo V, Ambrosio L. Influence of gelatin cues in PCL electrospun membranes on nerve outgrowth. ACS PublicationsMA Alvarez-Perez, V Guarino, V Cirillo, L AmbrosioBiomacromolecules, 2010•ACS Publications [Internet]. 2010 Sep 13 [cited 2025 Nov 8];11(9):2238–46.

59. Terraf P, Kouhsari SM, Ai J, Babaloo H. Tissue-Engineered Regeneration of Hemisected Spinal Cord Using Human Endometrial Stem Cells, Poly ε-Caprolactone Scaffolds, and Crocin as a Neuroprotective Agent. Mol Neurobiol [Internet]. 2017;54(7):5657–67.

60. Babaloo H, Ebrahimi-Barough S, Derakhshan MA, Yazdankhah M, Lotfibakhshaiesh N, Soleimani M, et al. PCL/gelatin nanofibrous scaffolds with human endometrial stem cells/Schwann cells facilitate axon regeneration in spinal cord injury. J Cell Physiol. 2019 Jul 1;234(7):11060–9.

61. Rose JB, Sidney LE, Patient J, White LJ, Dua HS, El Haj AJ, et al. In vitro evaluation of electrospun blends of gelatin and PCL for application as a partial thickness corneal graft. J Biomed Mater Res A. 2019 Apr 1;107(4):828–38.

62. Fernández-Pérez J, Kador KE, Lynch AP, Ahearne M. Characterization of extracellular matrix modified poly(ε-caprolactone) electrospun scaffolds with differing fiber


https://doi.org/10.22034/jrb.2025.12.V1I4A4

orientations for corneal stroma regeneration. Materials Science and Engineering C. 2020 Mar 1;108.

63. Schubert DW. Mechanical and Optical Properties of PCL Nanofiber Reinforced Alginate Hydrogels for Application in Corneal Wound Healing. 2018;

64. Baradaran-Rafii A, Biazar E, Heidari-Keshel S. Cellular Response of Limbal Stem Cells on Polycaprolactone Nanofibrous Scaffolds for Ocular Epithelial Regeneration. Curr Eye Res [Internet]. 2016 Mar 3 [cited 2025 Nov 9];41(3):326–33.

65. Tandon R, Singh H, Mohanty S, Gupta D, Jassal M, Agarwal A. Ex - vivo cultivation of limbal epithelial cells and corneal stromal cells on electrospun plasma treated poly-ε-caprolactone scaffolds for ocular surface reconstruction. Invest Ophthalmol Vis Sci. 2014 Apr 30;55(13):5181–5181.

66. Sharma S, Mohanty S, Gupta D, Jassal M, Agrawal AK, Tandon R. Cellular response of limbal epithelial cells on electrospun poly-ε-caprolactone nanofibrous scaffolds for ocular surface bioengineering: a preliminary in vitro study. Mol Vis [Internet]. 2011 [cited 2025 Nov 9];17:2898.

67. Carter K, Lee HJ, Na KS, Fernandes-Cunha GM, Blanco IJ, Djalilian A, et al. Characterizing the impact of 2D and 3D culture conditions on the therapeutic effects of human mesenchymal stem cell secretome on corneal wound healing in vitro and ex vivo. Acta Biomater [Internet]. 2019 Nov 1 [cited 2025 Nov 9];99:247–57.

68. Moazzami Goudarzi Z, Behzad T, Ghasemi-Mobarakeh L, Kharaziha M. An investigation into influence of acetylated cellulose nanofibers on properties of PCL/Gelatin electrospun nanofibrous scaffold for soft tissue engineering. Polymer (Guildf) [Internet]. 2021 Jan 20 [cited 2025 Nov 9];213:123313.

69. Feng Y, Jupei Z, Dong Z, Tang L. Characterization, biocompatibility, and optimization of electrospun SF/PCL composite nanofiber films. Reviews on Advanced Materials Science [Internet]. 2023 Jan 1 [cited 2025 Nov 9];62(1).

70. Chandika P, Oh GW, Heo SY, Kim SC, Kim TH, Kim MS, et al. Electrospun porous bilayer nano-fibrous fish collagen/PCL bio-composite scaffolds with covalently cross-linked chitooligosaccharides for full-thickness wound-healing applications. Materials Science and Engineering: C [Internet]. 2021 Feb 1 [cited 2025 Nov 9];121:111871.

71. Rashtchian M, Hivechi A, Bahrami SH, Milan PB, Simorgh S. Fabricating alginate/poly(caprolactone) nanofibers with enhanced bio-mechanical properties via cellulose nanocrystal incorporation. Carbohydr Polym [Internet]. 2020 Apr 1 [cited 2025 Nov 9];233:115873. \

72. Sadeghianmaryan A, Karimi Y, Naghieh S, Alizadeh Sardroud H, Gorji M, Chen X. Electrospinning of Scaffolds from the Polycaprolactone/Polyurethane Composite with Graphene Oxide for Skin Tissue Engineering. Applied Biochemistry and Biotechnology 2019 191:2 [Internet]. 2019 Dec 10 [cited 2025 Nov 9];191(2):567–78.

73. Unalan I, Slavik B, Buettner A, Goldmann WH, Frank G, Boccaccini AR. Physical and Antibacterial Properties of Peppermint Essential Oil Loaded Poly (ε-caprolactone) (PCL) Electrospun Fiber Mats for Wound Healing. Front Bioeng Biotechnol [Internet]. 2019 Nov 26 [cited 2025 Nov 9];7:488792.

74. Mohamed SA, Elsherbini AM, Alrefaey HR, Adelrahman K, Moustafa A, Egodawaththa NM, et al. Gum Arabic: A Commodity with Versatile Formulations and Applications. Nanomaterials 2025, Vol 15, [Internet]. 2025 Feb 13 [cited 2025 Nov 9];15(4).

75. Pedram Rad Z, Mokhtari J, Abbasi M. Calendula officinalis extract/PCL/Zein/Gum arabic nanofibrous bio-composite scaffolds via suspension, two-nozzle and multilayer electrospinning for skin tissue engineering. Int J Biol Macromol [Internet]. 2019 Aug 15 [cited 2025 Nov 9];135:530–43.

76. Baghersad S, Hivechi A, Bahrami SH, Brouki Milan P, Siegel RA, Amoupour M. Optimal Aloe vera encapsulated PCL/Gel nanofiber design for skin substitute application and the evaluation of its in vivo implantation. J Drug Deliv Sci Technol [Internet]. 2022 Aug 1 [cited 2025 Nov 9];74.

77. Rahmani Del Bakhshayesh A, Mostafavi E, Alizadeh E, Asadi N, Akbarzadeh A, Davaran S. Fabrication of Three-Dimensional Scaffolds Based on Nano-biomimetic Collagen Hybrid Constructs for Skin Tissue Engineering. ACS Omega [Internet]. 2018 Aug 31 [cited 2025 Nov 9];3(8):8605–11.

78. Asadi N, Alizadeh E, Rahmani Del Bakhshayesh A, Mostafavi E, Akbarzadeh A, Davaran S. Fabrication and in Vitro Evaluation of Nanocomposite Hydrogel Scaffolds Based on Gelatin/PCL–PEG–PCL for Cartilage Tissue Engineering. ACS Omega [Internet]. 2019 Jan 7 [cited 2025 Nov 9];4(1):449–57.

79. Fereshteh Z, Fathi M, Bagri A, Boccaccini AR. Preparation and characterization of aligned porous PCL/zein scaffolds as drug delivery systems via improved unidirectional freeze-drying method. Materials Science and Engineering C [Internet]. 2016 Nov 1 [cited 2025 Nov 9];68:613–22.

80. Salerno A, Domingo C, Saurina J. PCL foamed scaffolds loaded with 5-fluorouracil anti-cancer drug prepared by an eco-friendly route. Mater Sci Eng C Mater Biol Appl [Internet]. 2017 Jun 1 [cited 2025 Nov 9];75:1191–7.

81. Seyed Hakim R, Maghsoud Z, Halabian R. Fabrication and evaluation of polycaprolactone/olive oil scaffolds by phase inversion for tissue engineering. Eur Polym J [Internet]. 2021 May 5 [cited 2025 Nov 9];150.

82. Jing X, Mi HY, Cordie T, Salick M, Peng XF, Turng LS. Fabrication of porous poly(ε-caprolactone) scaffolds containing chitosan nanofibers by combining extrusion foaming, leaching, and freeze-drying methods. Ind Eng Chem Res. 2014 Nov 19;53(46):17909–18.

83. Yao Z, Chen Z, He X, Wei Y, Qian J, Zong Q, et al. Bioactive MgO/MgCO3/Polycaprolactone Multi-gradient Fibers Facilitate Peripheral Nerve Regeneration by Regulating Schwann Cell Function and Activating Wingless/Integrase-1 Signaling. Advanced Fiber Materials [Internet]. 2025 Feb 1 [cited 2025 Nov 11];7(1):315–37.


https://doi.org/10.22034/jrb.2025.12.V1I4A4