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Review Article

NANOCELLULOSE-ENHANCED POLY (LACTIC-CO-GLYCOLIC) ACID AS A SYNTHETIC GRAFT MATERIAL FOR IMPROVED BONE AUGMENTATION: A SYSTEMATIC REVIEW

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ABSTRACT

A pre-implantation bone graft provides structural support when alveolar bone is insufficient. This study investigates nanocellulose and poly(lactic-co-glycolic acid) (PLGA) as grafting materials. PLGA enhances scaffold degradability through hydrolytic cleavage, with degradation kinetics determined by its lactic acid to glycolic acid (LA: GA) ratio. A 50:50 ratio degrades fastest (~8 w), while a 75:25 ratio slows degradation (~16 w). Nanocellulose, while being poorly degradable *in vivo*, improves mechanical strength and hydrophilicity. PLGA/CNF scaffolds showed 95% porosity with through-pores (20–100 µm), promoting cell infiltration. Mechanical strength improved with nanocellulose: compressive strength increased from 4.0 MPa (PLGA) to 6.4 MPa (PLGA/CMC), and elastic modulus reached 1,240±40 MPa in PVA/PLGA/CNC composites—a 42-fold increase. Good biocompatibility was found in all the composite samples examined, and osteogenesis was promoted. *In vitro* and *in vivo* studies confirmed that PLGA compensates for nanocellulose's limited degradability, with complete scaffold resorption observed within 12 w for 50:50 PLGA and within three months for CPC/PLGA/CMC in PBS. These results highlight the synergistic potential of PLGA/nanocellulose composites for bone tissue engineering by combining tunable degradability, enhanced mechanics, and strong biocompatibility.

Keywords: Nanocellulose, Poly(lactic-co-glycolic) acid/PLGA, Polymer, Synthetic graft, Bone augmentation

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INTRODUCTION

Failure of dental implant is often linked to inadequate volume of alveolar bone in the edentulous area [1, 2]. This deficiency may arise from factors such as bone resorption or atrophy, which can be consequences of tooth extraction, periodontal disease, trauma, accidents, or tumor removal [3]. Such conditions make it difficult to place dental implants in a stable and ideal position [4]. To address this issue, bone augmentation through bone grafting is a commonly performed preparatory procedure for dental implants aimed at enhancing the density and volume of the alveolar bone, thereby providing better support for dental implants [3].

Bone grafting plays a crucial function in enhancing bone volume as it serves as a scaffold that creates a biological environment similar to natural bone, promoting new tissue formation [5]. When applied in bone augmentation, bone grafts establish a three-dimensional framework in the regeneration area, enabling osteoblast cells to migrate, adhere, proliferate, and differentiate effectively [6]. This process follows the principle of osteoconduction, which is fundamental to bone regeneration [7]. Osteoconduction relies on several key factors, including biocompatibility, a porous three-dimensional structure, biodegradability, integration with surrounding tissues through hydrophilicity, and mechanical strength for stability [6, 8]. Researchers are continually exploring various biosynthetic materials to develop bone grafts that meet all osteoconduction criteria [9].

In addition to osteoconduction, two other essential principles of bone regeneration are osteogenesis and osteoinduction [6, 10]. The ability of the bone graft to supply osteogenic cells, including osteoblasts or Mesenchymal Stem Cells (MSCs), to the regeneration site is known as osteogenesis [6, 10, 11]. These osteogenic cells can be introduced by cell transplantation or come from the graft itself, as in autografts or allografts [10]. Osteoinduction, on the other hand, is the process by which a bone graft stimulates MSCs to transform into cells responsible for bone formation [6, 10, 11]. This capability relies on the availability of growth factors in the graft or the roughness of its surface, both of which influence cellular attachment and differentiation [6, 12].

Poly(lactic-co-glycolic) acid (PLGA) refers to a synthetic polymer produced through the copolymerization of poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) [13, 14]. A study emphasizes the promise of PLGA in cancer treatment via targeted drug delivery, combinatorial therapies, and immunotherapy [15]. PLGA also has gained widespread use in tissue regeneration and has received approval from both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [16-18]. The composition of PLGA is determined based on the proportion of Lactic Acid (LA) to glycolic acid (GA), which directly influences its properties. For instance, a PLGA 75:25 composition indicates an increased ratio of glycolic acid [13]. The distinct characteristics of LA and GA result in varying properties of PLGA. LA exhibits biocompatibility, strong antibacterial effects, and hydrophobicity, whereas GA is hydrophilic and degrades rapidly [19, 20]. PLGA is frequently utilized in tissue regeneration due to its compatibility with biological systems, modifiable degradation rate, and minimal toxicity [16, 19]. Additionally, PLGA structures at the micro-and nanoscale serve as controlled release systems, enabling the regulation of osteogenic and osteoinductive properties by delivering stem cells or growth factors [21]. A study highlighted that PLGA scaffolds are widely used in tissue regeneration because they are safe for the body, support cell growth, and can mimic the natural structure of tissues—especially when coated with collagen or extracellular matrix proteins [22]. However, PLGA possesses certain drawbacks, including its hydrophobic nature and mechanical strength, which is considerably reduced than that of natural bone [13, 16, 23]. Its hydrophobicity limits protein and cell adhesion, making cell regeneration inside the graft more challenging [14]. To overcome these limitations, PLGA is often integrated with additional substances to enhance its effectiveness in tissue regeneration. Studies have explored the reinforcement of PLGA with substances like Hydroxyapatite (HA) and Bioglass (BG) to enhance its mechanical strength [13, 14].

Nanocellulose is a naturally abundant polymer that is easily sourced, making it a cost-effective option. It is a hydrophilic polysaccharide that can be obtained from various biological origins, including plants, bacteria, and algae [24, 25]. The primary forms of nanocellulose utilized in bone augmentation are Cellulose Nanocrystal (CNC), Cellulose Nanofiber (CNF), Bacterial Cellulose (BC), Carboxymethyl Cellulose (CMC), and Hydroxypropyl Methylcellulose (HPMC) [24, 26]. Due to its nanoscale structure, nanocellulose exhibits improved properties compared to conventional cellulose, including low toxicity, rapid degradation, and prolonged angiogenesis [24]. It exhibits multiple qualities advantageous for tissue regeneration, including biocompatibility, non-toxicity, a porous three-Dimension (3D) structure, hydrophilicity, resilience, rigidity, and exceptional mechanical strength [12, 24, 25, 27]. Specifically, nanocellulose demonstrates exceptional mechanical properties, including high density, an elevated elastic modulus, superior tensile strength, and an outstanding strength-to-weight ratio [24, 27]. Research conducted by Deng *et al.* suggests that cellulose and its derivatives hold potential for bone repair; however, certain challenges still need to be addressed [28]. CNC, especially when surface-modified with cationic groups, can trigger immune responses such as lysosomal damage and inflammasome activation, leading to inflammation [29]. CNCs around 200–300 nm in length were particularly effective at stimulating immune cells, highlighting the impact of size and surface chemistry on their biological activity [30,31]. Mandai *et al.* reported that bacterial CNF films are biocompatible but degrade unpredictably in the body, limiting their use in applications like wound dressings that require controlled resorption [32]. In addition, CNC produced via sulfuric acid hydrolysis may impair biocompatibility due to sulfate groups, while enzymatically derived CNC shows low cytotoxicity [33]; similarly, bacterial CNF is generally safe but can reduce cell viability and cause inflammation at high concentrations [29].

Nanocellulose's superior mechanical strength supports its frequent integration with other biomaterials—such as Polylactic Acid (PLA), Polyvinyl Alcohol (PVA), silk fibroin, Biphasic Calcium Phosphate (BCP), and chitosan—to enhance structural integrity and biological performance [12, 13]. PLA/CNC has been shown to stimulate the expression of Transforming Growth Factor (TGF-β1), thereby supporting osteoinductive processes crucial for bone tissue regeneration [34]. Costa *et al.* showed that bacterial nanocellulose (BNC) has adjustable porosity and a large surface area for controlled drug release, and when combined with the biodegradable properties of PLGA, the resulting composite system holds potential for prolonged and efficient drug delivery systems [35]. Another review study highlighted PLGA/Ag_2O nanocomposites for their strong antibacterial activity and cell compatibility, suggesting that nanocellulose's natural antimicrobial properties could similarly enhance PLGA-based materials for surgical application [36]. Findings by Mo *et al.* support the potential of PLGA–nanocellulose composites as effective membranes for guided bone regeneration [23]. This study reported improvements in membrane thickness, surface roughness, hydrophilicity, thermal stability, and mechanical strength when nanocellulose was incorporated into PLGA, compared to PLGA alone [23]. In addition, other study demonstrated that reinforcing PLGA membranes with nanocellulose, which possesses high tensile strength (10–20 GPa) and stiffness (110–220 GPa), has been shown to compensates for PLGA's inherent brittleness while maintaining biocompatibility, making the composite suitable for bone regeneration membranes [37]. Nevertheless, nanocellulose also presents certain drawbacks that may affect its functionality as a bone graft material. These challenges include a slow degradation rate in most nanocellulose types, non-degradability in bacterial nanocellulose, and potential immunogenicity in CNC [27, 37].

The combination of nanocellulose with PLGA presents a promising strategy for enhancing mechanical strength and hydrophilicity in bone graft applications. Sukul *et al.* demonstrated that incorporating nanocellulose into bone grafts enhances their mechanical performance and increases surface area, thereby facilitating improved protein adsorption and cellular adhesion [38]. However, nanocellulose's rigidity posed clinical handling challenges, which the hybrid material mitigated by balancing flexibility and strength. Consequently, ongoing studies are centered on enhancing the capability of nanocellulose in bone tissue engineering. These findings suggest that combining PLGA and nanocellulose could create a synergistic effect, addressing the limitations of both materials and improving their overall functionality as bone grafts [23, 39].

Objective

This research aimed to evaluate the feasibility of using nanocellulose-reinforced PLGA as a grafting material for enhancing bone regeneration.

Method

Study design

The research was carried out following the guidelines specified in The Preferred Reporting Items for Systematic Review and Meta-Analysis-Rapid Review (PRISMA-RR). This systematic review was limited to peer reviewed original research articles with *in vivo*, *in vitro*, or *ex vivo* experimental research with biological, mechanical or histological evaluations, as such studies provide fundamental primary data needed for evaluating the regenerative potential of biomaterials. The studies had to incorporate both PLGA and nanocellulose together in any form as parts, fibers, or scaffolds. Studies that evaluated either material separately were not considered in order to assess the synergistic effects of both PLGA and nanocellulose. The application area was restricted to scaffold-based approaches for tissue engineering bone, which includes bone grafting and scaffolding. Studies were included only if the materials were designed to structurally and biologically fill spaces through which new bone would grow, thus functioning as load-bearing osteoconductive scaffolds. Studies that were solely about membranes were excluded, because barrier membranes serve only to hinder the ingrowth of soft tissues and do not possess the bone structural properties which are critical for bone regeneration. Likewise, non-bone related works such as wound healing or cartilage regeneration were excluded as they are part of entirely different biological environments and design frameworks. Only articles published in English in the last twenty years (2004-2024) were considered, due to language translation limitations and the need for consistent and accurate data extraction. Systematic reviews or meta-analyses were included only when they presented data that allowed for the identification and tracking of relevant original studies.

Articles that did not meet these criteria were excluded, such as systematic reviews, meta-analyses, inaccessible publications, and studies discussing PLGA/nanocellulose in membrane applications rather than scaffolds. Studies were excluded if they focused solely on membrane-based applications, such as barrier membranes used in guided bone regeneration, without addressing scaffolds with osteoconductive or load-bearing functionality. These membranes serve a different regenerative role and do not meet the structural or biological criteria set for scaffold-based bone regeneration. Research that focused on non-bone tissue engineering applications—including those targeting cartilage, nerve, skin, or periodontal tissues—was also excluded, as these involve distinct mechanisms of healing and material design requirements. In addition, studies that evaluated only one of the two materials (PLGA or nanocellulose) without their combined use were excluded, since the aim was to investigate outcomes resulting specifically from their synergistic application. Conference abstracts, editorials, and patents were also excluded due to their lack of detailed methodology, incomplete data, or absence of peer review, which limits their reliability for inclusion in a systematic review.

Literature research and data extraction

A comprehensive literature search was conducted across seven major academic journal databases, including PubMed NCBI, ScienceDirect, Scopus, Springer, Cochrane, and Open DOAJ. The advanced search strategy incorporated a combination of key terms such as "poly(lactic-co-glycolic acid)," "nanocellulose," "bacterial nanocellulose," "CNF" (cellulose nanofibrils), "CNC" (cellulose nanocrystals), "HMPC," and "CMC," in conjunction with terms like "bone graft" and "scaffold" to target relevant studies. Boolean operators (AND/OR) were applied to optimize and refine search results for precision and relevance. The specific search string used was ("poly(lactic-co-glycolic acid)" OR "PLGA") AND ("nanocellulose" OR "cellulose nanocrystal*" OR "cellulose nanofibril*" OR "bacterial nanocellulose") AND ("bone graft" OR "bone regeneration" OR "bone tissue engineering" OR "osteogenic

scaffold" OR "bone scaffold") NOT ("membrane" OR "dental" OR "periodontal" OR "oral surgery"). This strategy ensured the inclusion of studies focused on the combined application of PLGA and nanocellulose in bone-related scaffold development, while excluding research outside the scope of interest, such as those focused on dental membranes or non-bone tissues.

Table 1: The usage of PLGA reinforced by nanocellulose as bone graft materials

Authors (Year)	Title of the article	Type of study	Bone graft material	Results				
				Material testing				
				Porous structure	Hydrophilicity	Mechanical strength	Biocompatibility	Degradation rate and duration
Rescignano *et al.* (2014) [58]	PVA bio-nanocomposites: a new take-off using cellulose nanocrystals and PLGA nanoparticles	Material testing, *in vitro*	PVA/PLGA 50:50/CNC	The use of electrospinning typically creates fibrous, porous architectures. The addition of PLGA nanoparticles might introduce nano-scale pores	The 50:50 PLGA ratio and PVA is hydrophilic, combined with PVA and CNCs amplified the composite's hydrophilicity	Incorporation of CNC: elastic modulus increased Elastic modulus: 1,240±40 Mpa.	Non-toxic towards hBM-MSCs	Completely degraded after 45 min soaked in 37 °C water
Tang et al. (2017) [18]	Biodegradable tissue engineering scaffolds based on nanocellulose/ PLGA nanocomposite for NIH 3T3 cell cultivation/PLGA nanocomposite for NIH 3T3 cell cultivation	Material testing, in vitro	PLGA 75:25/CNF	Porosity level: 95% Porous size: 20–100 µm Interconnected porous structure. Incorporation of CNF: nanonetwork of porous increased. Incorporation of CNF: hydrophilicity increased	Incorporation of CNF: compressive strength and elastic modulus increased. Elastic modulus: 10.64–16.54 Kpa. Compressive strength: 4.385–8.245 Kpa.	Facilitate fibroblast NIH/3T3 cell growth and proliferation. Incorporation of CNF: surface roughness increased	Non-toxic towards H9 cells.	Degradable
Qutachi *et al.* (2018) [53]	Improved delivery of PLGA microparticles and microparticle-cell scaffolds in clinical needle gauges using modified viscosity formulations	Material testing, *in vitro*	PLGA 50:50/CMC/ pluronic F127	Implied microparticulate porous structure that is conducive to cell attachment and transport	Incorporation of CMC/pluronic F127: hydrophilicity increased	Not directly measured, however significantly enhanced microparticle delivery efficiency, improved flow and suspension stability rather than intrinsic mechanical reinforcement	Viability cell testing using BMSCs reported a great result. Incorporation of CMC/pluronic F127: cell delivery increased.	Exact degradation rates were not quantified. However, PLGA with Pluronic F127 potentially accelerating degradation
Patel *et al.* (2020) [34]	Bioactive electrospun nanocomposite scaffolds of poly(lactic acid)/cellulose nanocrystals for bone tissue engineering	Material testing, *in vitro*, *in vivo*	PLA: CNC	PLA/CNC composites exhibit higher porosity	Incorporation of CNC: hydrophilicity increased	Incorporation of<4% CNC: elastic modulus increased Incorporation of 4% CNC: elastic modulus decreased	No complication occurred to the BMSCs. Incorporation of CNC: *in vivo* viability cell, osteogenic potential of BMSCs, osteogenic differentiation and osteogenic efficiency increased J17. No inflammation occurred during 3 w post-transplantation on rat calvarial bone. Incorporation of CNC: *in vivo* osteogenic efficiency increased.	Incorporation of CNC into PLA enhanced the degradation rate
Cai *et al.* (2022) [54]	Injectable nanofiber-reinforced bone cement with controlled biodegradability for minimally-invasive bone regeneration	Material testing, *in vitro*, *in vivo*	CPC/PLGA 85:15/CMC	The porous structure of CPC/PLGA/CMC> CPC Porous size:>100 µm	CMC incorporation into CPC/PLGA composites increases hydrophilicity	Compressive strength CPC/PLGA/CMC: 6.4±0.2 MPa, a 30% increase compared to CPC	Biocompatible with the rat femur bone Facilitate BMSCs adhesion and proliferation Facilitate osteogenic differentiation Facilitate angiogenesis	Degradation rate CPC/PLGA/CMC> CPC Fully degraded three months post-implantation

PLGA: Poly(lactic-co-glycolic) acid; PVA: Polyvinyl Alcohol; CNC: Cellulose Nanocrystal; hBM-MSCs: human Bone Marrow-Mesenchymal Stem Cells; CNF: Cellulose Nanofiber; NIH3T3: National Institutes of Health 3-day transfer, inoculum 3 × 105 cells" (Todaro and Green 1963) (mouse embryonic fibroblast cells); HUVECs: Human Umbilical Vein Endothelial Cells; PLA: Poly(Lactic Acid); CMC: Carboxymethyl Cellulose; BMSCs: Bone Marrow Stromal Cells; CPC: Calcium Phosphate Cement; MPa: Megapascal; KPa: Kilopascal; µm: micrometer.

The selection and screening of relevant articles followed the PRISMA framework (fig. 1), and relevant data extracted from each article. For original experimental studies, risk of bias was assessed based on criteria such as study design, control conditions, sample size, and reporting of outcomes. The data extraction process followed a structured protocol in which publication year, authorship, study design, materials used, scaffold composition, PLGA:nanocellulose ratio, and key findings were recorded. In cases of conflicting or heterogeneous findings—such as differences in PLGA composition, nanocellulose type, or scaffold fabrication techniques—data were reconciled through comparison against the inclusion criteria and by assessing study quality and relevance. When needed, subgroup analysis or narrative synthesis was used to account for methodological differences and ensure accurate interpretation of the outcomes within the defined scope of this review.

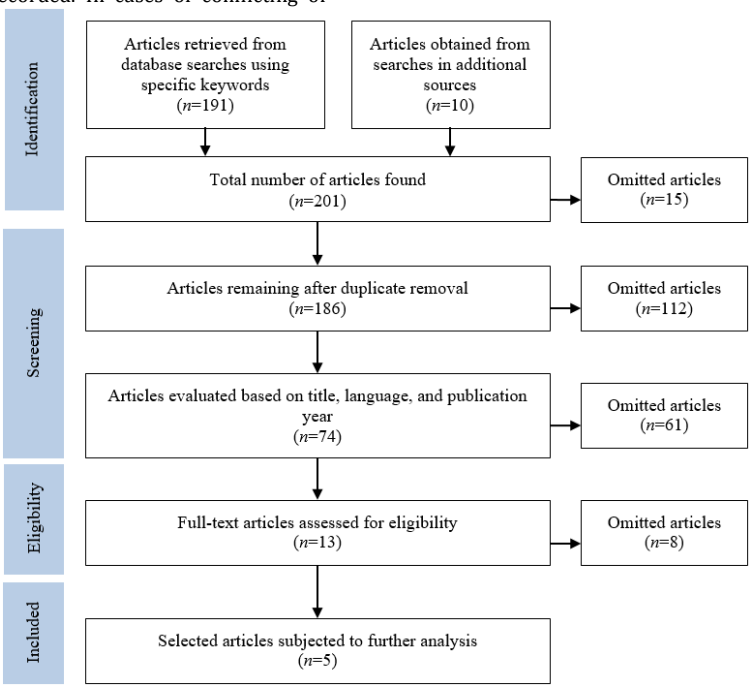

Fig. 1: Flowchart of PRISMA

RESULTS

A total of 201 articles were initially identified through systematic database searches and supplementary sources. Of these, 15 articles were immediately excluded due to irrelevance or inaccessible full text, leaving 186 articles for further screening. After removing duplicates, the screening process continued with 186 unique records. At this stage, 112 articles were excluded based on titles, abstracts, and keywords. The primary reasons for exclusion included a lack of relevance to bone tissue engineering (e. g., focus on cartilage, skin, or periodontal tissues), absence of scaffold-based applications (such as studies involving only membranes or injectable systems), or the use of only one material—either PLGA or nanocellulose-without combining both, which was essential for evaluating their synergistic effects.

The remaining 74 articles were then evaluated for eligibility based on title relevance, publication language, and publication year. An additional 61 articles were excluded due to being outside the 2004–2024 publication window, being published in languages other than English, and involving only one of the two target materials. This left 13 full-text articles for detailed assessment. Of these, 8 were excluded due to lack of focus on load-bearing scaffold applications, insufficient methodological quality, and because they addressed non-bone tissue regeneration contexts. Some were also review articles lacking traceable original data.

The article selection process, based on the PRISMA framework, identified five studies that aligned with the established selection and elimination criteria. These research studies explored the integration of PLGA and nanocellulose, either independently or in conjunction with other materials, as scaffold elements for bone regeneration and tissue repair (table 1). The results were divided into two primary groups: material characterization and biological assessments carried out through *in vitro* and *in vivo* studies. Material characterization analyzed attributes like porosity, hydrophilicity, and mechanical properties, whereas *in vitro* and *in vivo* evaluations focused on biocompatibility and biodegradability. Each of these factors was thoroughly investigated to assess the suitability of these materials for bone graft applications.

DISCUSSION

Bone augmentation through bone grafting is a technique designed to restore bone tissue in regions affected by bone deficiency, utilizing graft materials to facilitate and support the regeneration process [40, 41]. Bone grafts are generally required when bone defects exceed 8 mm, as smaller defects can naturally heal through the bone remodeling process [12]. Significant alveolar bone defects may arise due to post-extraction resorption, periodontal diseases (such as periodontitis and dental abscesses), traumatic injuries (resulting from accidents in traffic, workplaces, or sports), tumor removal, congenital abnormalities, or jaw atrophy caused by aging or disease [6, 42].

Frequently utilized types of bone grafts consist of autografts, xenografts, and alloplastic materials. [7]. Autografts are harvested from the recipient's own body, while allografts come from a donor [7]. Xenografts, on the other hand, are derived from animal bones [3,41]. Alloplastic grafts, made from synthetic biomaterials, serve as an alternative to natural grafts due to their ability to be mass-produced and their lack of disease transmission risks associated with biological sources [9]. An effective bone graft material must possess key properties that support bone regeneration, including porosity, hydrophilicity, sufficient mechanical strength, biocompatibility, and degradability. These characteristics are essential to fulfill the osteoconductive principle. The following section provides an in-depth analysis of the material testing results for PLGA, nanocellulose, and their combination as bone graft materials.

Material testing analysis result

Material testing covers key aspects such as porosity, hydrophilicity, and mechanical properties. The porous structure of a bone graft is

essential for promoting bone regeneration while also enabling the transfer of nutrients and metabolic waste products. To ensure effective cell migration and growth, the pore size should be a minimum of 100 µm with an ideal range between 200-800 µm [6, 38]. Additionally, bone graft materials must exhibit a porosity level of at least 50% of their total volume [6]. The wettability of the material, or its hydrophilicity, plays a crucial role in allowing cells to adhere to its surface [8]. Furthermore, the mechanical properties of the graft should align with the strength requirements necessary to support new tissue formation and maintain structural integrity [18, 44]. Specifically, for alveolar bone augmentation, graft materials must exhibit compressive strength and an elastic modulus comparable to that of cortical bone [6]. Generally, the cortical bone exhibits a compressive strength ranging from 100 to 200 MPa, with an elastic modulus falling between 15 and 20 GPa [45].

Porous structure

A porous framework plays a vital role in tissue regeneration by allowing new cells to migrate to the damaged area [6, 19]. Scaffolds with highly porous architectures are particularly effective in supporting tissue formation by enhancing cellular interactions and integration [46]. A well-connected porous network facilitates nutrient delivery and waste removal, further promoting tissue regeneration [47].

Both nanocellulose and PLGA inherently possess a porous internal architecture. Previous studies revealed that PLGA demonstrates an advantageous porosity level of approximately 85–95% [44, 48, 49]. Moreover, its pore size and interconnectivity can be adjusted depending on the manufacturing method [44, 48, 49]. For instance, Duan *et al.* engineered a PLGA-based double-layered bone graft with distinct pore sizes in each layer [44]. Similarly, nanocellulose is recognized as a suitable scaffold material because of its natural porosity. Favi *et al.* developed bacterial cellulose (BC) bone grafts, which, although porous, exhibited pore sizes smaller than those recommended for bone augmentation, making them better suited for connective tissue repair [50]. Additional studies incorporating nanocellulose combined with substances like nano-hydroxyapatite and hydroxyapatite/chitosan has been documented the formation of irregularly interconnected porous networks [51,52]. Additionally, the integration of nano-hydroxyapatite (n-HA) with cellulose-graft-polyacrylamide (CP) was found to produce a porous structure with properties closely resembling those required for bone regeneration [51].

The integration of PLGA and nanocellulose as a composite bone graft material has demonstrated promising porosity characteristics. Earlier studies confirmed the presence of a well-structured porous network within these scaffolds [18, 53, 54]. In particular, the PLGA/CNF scaffold exhibited a high porosity level of 95%, with well-interconnected pores ranging from 20–100 µm in size [18]. Furthermore, Calcium Phosphate bone Cement (CPC) or PLGA or CMC scaffolds displayed even greater porosity than CPC alone, with pore sizes exceeding 100 µm [52].

Hydrophilicity

PLGA naturally exhibits hydrophobic properties, which reduce its suitability as a bone graft material by restricting the adhesion of new bone cells [13, 14]. However, studies have shown that modifying PLGA can improve its hydrophilicity. For example, Rasoulianboroujeni *et al.* enhanced PLGA's wettability by incorporating TiO_2 [55]. Conversely, nanocellulose is naturally hydrophilic [25]. Research on CNC/BG bone grafts demonstrated that the addition of CNC significantly increased hydrophilicity [56]. Similarly, studies on PLGA and nanocellulose composites revealed improved wettability. These studies successfully reduced the hydrophobic nature of PLGA by integrating CNF, CMC/pluronic F12, and CNC, respectively [18, 34, 53].

Mechanical strength

One of PLGA's major limitations is its insufficient mechanical strength [13, 14]. Previous study observed that bone grafts made from PLGA exhibited low compressive strength, ranging from 4 to 5 MPa. Similarly, other study by Duan *et al.* found that their PLGA scaffold had an elastic modulus of 28.9 MPa, which falls below the optimal level required for effective bone regeneration [44, 48]. Consequently, PLGA must be reinforced with additional substances to enhance its structural characteristics. Previous studies indicated that integrating HA and Titanium Dioxide (TiO_2) into PLGA scaffolds substantially strengthened their mechanical characteristics [55, 57].

In contrast, nanocellulose demonstrates outstanding mechanical durability. Research by Favi *et al.* revealed that bone grafts derived from BC possessed mechanical characteristics similar to natural bone [50]. Similarly, the CP/n-HA composite displayed mechanical characteristics comparable to trabecular bone [51]. Chen *et al.* also observed that adding CNC to CNC/BG bone grafts improved their mechanical properties [56]. Based on these findings, nanocellulose appears to be a suitable reinforcing agent for PLGA in bone graft applications.

Research by Rescignano *et al.* indicated that incorporating nanocellulose into a PVA/PLGA/CNC scaffold induced a crystallization effect, leading to enhanced elasticity and reduced plasticity. The elastic modulus of this composite was measured at 1,240±40 MPa [58]. Additionally, CPC/PLGA/CMC scaffolds exhibited a 30% increase in mechanical strength (6.4±0.2 MPa) compared to CPC alone after the inclusion of CMC [54]. Tang *et al.* reported that reinforcing PLGA with CNF improved its mechanical properties, resulting in compressive strength and elastic modulus values approaching those of cartilage (4.385–8.245 KPa and 10.64–16.54 KPa, respectively) [18]. Furthermore, increasing the CNF concentration in the scaffold was found to further enhance mechanical strength [18]. However, Patel *et al.* noted that when CNC concentration exceeded 4%, the elastic modulus of the scaffold decreased [34]. Patel *et al.* reported that CNC reduced elastic modulus above 4% reflects a common nanocomposite limitation due to nanoparticle agglomeration, indicating an optimal CNC loading near 3–4%. Their PLA/CNC composite's compressive strength (~6.4 MPa) remains well below natural bone, limiting clinical use to non-load-bearing applications. The stark contrast in degradation times between PVA/PLGA/CNC and CPC/PLGA/CMC composites is primarily governed by PLGA copolymer ratios (50:50 vs. 85:15) and nanocellulose type (CNC vs. CMC), affecting hydrophilicity and hydrolysis rates [34]. For clinical use, getting regulatory approval is generally easier when using well-established polymers like PLA and PLGA, since they are already approved by the FDA or EMA. However, adding nanocellulose can complicate the process because its properties can vary and there isn't enough long-term safety data yet. While methods like extrusion, 3D printing, and cement mixing can be scaled up for manufacturing, it's still challenging to maintain consistent quality, especially in terms of how evenly the materials are mixed and how reliable the mechanical properties are. Overall, these points show that while these composites have strong potential for medical applications, there are still some important hurdles to overcome.

***In vitro* or *in vivo* testing analysis result**

In vitro and *in vivo* evaluations assess key properties such as biocompatibility and degradability. A bone graft is considered biocompatible if no adverse local or systemic reactions occur [8]. This characteristic is further demonstrated by the material's capacity to facilitate cell attachment, movement, differentiation, growth, and functional integration within the graft framework [59]. Degradability is also a crucial factor, as it determines the graft's availability and lifespan. To eliminate the need for secondary surgical removal, bone grafts should naturally degrade after fulfilling their role in bone regeneration [9]. Ideally, the rate of degradation should correspond with the natural timeline of bone healing, which generally takes around 16–24 w [60].

Biocompatibility

Biocompatibility is essential for any bone graft material, as it ensures seamless integration with surrounding cells to facilitate tissue regeneration [8]. Previous studies highlight PLGA's outstanding biocompatibility, proving that it is non-toxic, does not trigger inflammatory responses, promotes the adhesion of bone marrow-derived stem cells (BMSCs), and supports osteogenesis and chondrogenesis while maintaining a controllable degradation rate [44, 48, 49]. Similarly, other studies has demonstrated nanocellulose's compatibility as a bone graft material, confirming its ability to support bone regeneration [50–52, 56, 61].

In vivo studies further validated the biocompatibility of PLGA/nanocellulose composite scaffolds. Across five separate studies, results consistently indicated effective biocompatibility, cell adhesion, and cell proliferation. The PVA/PLGA/CNC scaffold demonstrated non-toxicity and improved surface roughness, thereby enhancing cell attachment when evaluated with human bone marrow-mesenchymal stem cells (hBM-MSCs) [58]. Similarly, fibroblast NIH/3T3 cells successfully adhered and proliferated on PLGA/CNF scaffolds, with CNF integration increasing surface roughness and promoting better cell adhesion [18]. Additionally, the PLGA/CMC/pluronic F127 scaffold demonstrated good BMSCs viability and improved cell delivery [53].

Patel *et al.* evaluated the PLA/CNC scaffold using BMSCs *in vitro* and rat calvarial bone experiments *in vivo*. The results confirmed high cell viability with no complications, while CNC incorporation enhanced the osteogenic potential of BMSCs. A 4% CNC concentration was identified as optimal, significantly improving osteogenesis. *In vivo* testing further revealed effective bone defect healing in rats, without any indications of inflammation three weeks post-transplantation [34]. Cai *et al.* assessed the CPC/PLGA/CMC scaffold using BMSCs *in vitro* and rat femur bones *in vivo*. Their results indicated that BMSCs successfully attached and multiplied on the CPC surface, encouraging the development of new vascular structures. The scaffold also exhibited compatibility with rat bone tissue [54].

Degradability rate and duration

A bone graft's ability to degrade and integrate into the surrounding tissue is a vital characteristic, eliminating the requirement for an additional surgical intervention [9]. PLGA is well-known for its controlled degradability. Studies by Dai *et al.* and Duan indicated that PLGA bone grafts could undergo full degradation within 12 w, with partial degradation observed as early as 12 d [44, 48]. The rate at which PLGA degrades is influenced by its molecular weight and the proportion of lactic acid (LA) to glycolic acid (GA). Higher molecular weights extend degradation time, while a higher LA content increases hydrophobicity, thereby slowing degradation. The fastest degradation occurs with a 50:50 lA to GA ratio. Previous research has found that PLGA scaffolds with an 85:15 ratio degrade within eight weeks, whereas those with a 75:25 ratio take approximately 16 w [39].

On the other hand, nanocellulose does not degrade as efficiently as PLGA. Luo *et al.* observed that nanocellulose adapts well to biological environments but exhibits limited degradation *in vivo*, which affects absorption within the body [62]. Additionally, bone grafts incorporating CP/n-HA and HPMC/HA/Chitosan were reported to degrade at a slower rate, while BC-based bone grafts were found to be non-degradable [50–52]. Given these limitations, PLGA can potentially offset nanocellulose's degradation issues, making the composite material more viable.

The combination of PLGA and nanocellulose in scaffolds such as PVA/PLGA/CNC, PLGA/CNF, and CPC/PLGA/CMC has shown promising results, with successful degradation into surrounding tissues [18, 54, 58]. The PVA/PLGA/CNC scaffold completely disintegrated in water at 37 °C within 45 min [58]. In contrast, research indicated that the CPC/PLGA/CMC scaffold underwent complete degradation after being immersed in a phosphate-buffered saline (PBS) solution for three months [54].

Across various studies, the combination of PLGA and nanocellulose has demonstrated highly favorable outcomes in both material and biological testing. The inclusion of nanocellulose has successfully addressed PLGA's weaknesses, such as insufficient mechanical strength and hydrophobicity. Similarly, PLGA has maintained its controlled degradability despite nanocellulose's slower degradation rate. Furthermore, critical properties like porosity and biocompatibility have been preserved. While the PLGA/nanocellulose composite meets nearly all the necessary criteria for osteoconductivity, further refinement is required to enhance mechanical strength to its full potential.

CONCLUSION

This review highlights the promising potential of PLGA/nanocellulose composite scaffolds for use in alveolar bone augmentation. These materials meet several critical for bone regeneration, including high porosity, improved hydrophilicity, favorable biocompatibility, and controllable degradability. Among the nanocellulose types, cellulose nanocrystals (CNC) offer effective reinforcement when used at concentrations ≤ 4%, beyond which mechanical properties may deteriorate due to particle agglomeration. Despite these advantages, the mechanical strength of current composites remains significantly below that of natural cortical bone (100–200 MPa), limiting their application to non-load-bearing sites unless further enhanced through material or structural modifications.

Additionally, degradation rates vary depending on the PLGA copolymer composition and nanocellulose type, which can be advantageous for tailoring graft longevity to specific clinical needs. However, clinical translation faces notable hurdles, particularly regulatory approval challenges stemming from the lack of long-term safety data on nanocellulose and variability in its characterization. Moreover, while scalable fabrication methods exist, ensuring consistent nanocellulose dispersion and mechanical integrity at industrial levels remains difficult. A key limitation of this review is the reliance on heterogeneous studies that differ in scaffold composition, testing conditions, and evaluation metrics, making direct comparisons challenging. Therefore, future research should focus on standardizing composite formulations and conducting long-term *in vivo* studies to evaluate bone-regenerative capacity, host response, and scaffold degradation in physiological environments.

AUTHORS CONTRIBUTIONS

-Yunia Dwi Rakhmatia: Conceptualized the study, supervised the project, and contributed to manuscript writing and editing.

-Rifa Khalisha Indrawan: Conducted the literature search and data extraction, and contributed to manuscript writing.

-Lisda Damayanti: Participated in study design and analysis.

-Vita Mulya Passa Novianti: Contributed to data interpretation and manuscript editing.

-Novitri Hastuti: Provided critical revisions and final approval of the manuscript.

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CONFLICT OF INTERESTS

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