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From Oil Palm Biomass to Functional Regeneration: Translating Nanocellulose Scaffolds Across Tissue Engineering, Wound Healing, and Regenerative Rehabilitation—A Review

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Abstract

The conversion of agricultural residues into regenerative biomaterials creates an unusual intersection between circular bioeconomy, materials engineering, and regenerative medicine. Oil palm empty fruit bunches (OPEFB), a cellulose-rich residue generated in large quantities by the palm oil industry, have increasingly been investigated as feedstock for cellulose nanofibers, nanocellulose hydrogels, aerogels, and carboxymethyl-cellulose-based scaffolds. This qualitative literature review critically examines how oil-palm-derived cellulose materials could progress from biomass valorization toward tissue regeneration and functional recovery. Contemporary literature published predominantly from 2020 onward was interpreted across six interconnected themes: biomass-to-biomaterial transformation, scaffold structure–property relationships, cell–scaffold interactions, skin and wound regeneration, bone tissue engineering, and the mechanobiological transition from tissue repair to regenerative rehabilitation. Direct OPEFB evidence demonstrates high-porosity antibacterial bioaerogels supporting fibroblast proliferation and emerging cellulose-derived scaffolds supporting osteoblast attachment and proliferation. However, the evidence remains predominantly material-level and preclinical. Broader nanocellulose research shows how biomineralization, hybridization, surface modification, anisotropy, three-dimensional bioprinting, and mechanical conditioning could strengthen the regenerative functionality of oil-palm-derived scaffolds. The review proposes a biomass-to-function translational framework in which regenerative success requires not merely biocompatibility but coordinated achievement of biological integration, mechanical competence, safe degradation, manufacturing reproducibility, and rehabilitation-responsive tissue remodeling. Future studies should therefore connect sustainable material production with tissue-specific biological validation and functional outcomes.

Keywords: Oil Palm Biomass, Oil Palm Empty Fruit Bunch, Nanocellulose, Cellulose Nanofibers, Regenerative Biomaterials, Tissue Engineering, Wound Healing, Bone Regeneration, Mechanobiology, Regenerative Rehabilitation.

Introduction

The palm oil industry is usually discussed in relation to vegetable oil production, agricultural livelihoods, international trade, land use, and environmental sustainability. A less conventional but increasingly important perspective concerns the enormous quantity of lignocellulosic biomass that accompanies palm oil production.

Empty fruit bunches, mesocarp fibers, oil palm fronds, trunks, shells, and other residual streams contain fractions of cellulose, hemicellulose, lignin, and associated compounds that can be processed into increasingly sophisticated bio-based materials. Among these resources, oil palm empty fruit bunches (OPEFB) are particularly relevant because they are abundant, renewable, and cellulose-rich, yet their utilization remains substantially below their technological potential. Recent circular-bioeconomy research has therefore moved beyond treating OPEFB primarily as waste and has increasingly considered it a feedstock for chemicals, fuels, polymers, nanocellulose, hydrogels, and other high-value products [1, 2].

This transition is important because the value of agricultural biomass is not determined simply by the quantity diverted from disposal. A circular bioeconomy becomes progressively more sophisticated as biomass is converted into products with higher technological and social utility. OPEFB can be conceptualized along such a hierarchy: it may be used as bulk fibrous material, converted to fuels or chemicals, processed into cellulose, transformed into nanoscale cellulose, incorporated into engineered three-dimensional matrices, and potentially developed into biomedical scaffolds capable of interacting with living cells. In this sense, regenerative biomaterials represent an unusually high-value frontier of agricultural residue valorization because the objective is no longer merely substituting fossil-derived materials but contributing to tissue repair and human functional recovery [1-4]. Nanocellulose is particularly attractive within this progression. Depending on source and processing, nanoscale cellulose is commonly classified into cellulose nanocrystals (CNCs), cellulose nanofibrils or nanofibers (CNFs), and bacterial nanocellulose (BNC). These materials differ in dimensions, crystallinity, morphology, fabrication route, and surface characteristics, but they share several features that have encouraged biomedical investigation: high surface area, tunable chemistry, hydrophilicity, relatively strong mechanical performance at low mass, potential cytocompatibility, and compatibility with hydrogel, aerogel, composite, and bioink architectures. Recent syntheses additionally emphasize that surface modification, composite design, and process control determine whether these intrinsic advantages translate into useful scaffold performance [5-8]. Importantly, plant-derived CNF and CNC are not biologically or physicochemically identical to BNC. Source-specific processing, residual lignin or hemicellulose, chemical pretreatments, surface groups, fiber dimensions, contaminants, and sterilization history can substantially alter subsequent biological behavior [9].

The contemporary concept of a tissue-engineering scaffold has also evolved. Scaffolds were once frequently described primarily as structural supports that provided space in which cells could proliferate. Regenerative biomaterials are now expected to be considerably more sophisticated. Their pore architecture, stiffness, degradation, surface chemistry, topography, hydration, anisotropy, bioactive modification, and interaction with proteins influence cell attachment, migration, differentiation, extracellular matrix formation, inflammatory responses, vascularization, and remodeling. Consequently, a promising scaffold is not simply a porous object that does not kill cultured cells; rather, it constitutes a dynamic microenvironment that should support spatially and temporally coordinated regenerative processes [10-15]. Direct evidence connecting oil palm biomass to this regenerative-materials paradigm is still comparatively limited, but it is scientifically notable. Yahya et al. (2023) [16] converted OPEFB-derived cellulose nanofibers into highly porous bioaerogel scaffolds. Pure CNF aerogels exhibited particularly high porosity, water absorption, and surface area; chitosan improved mechanical characteristics, while incorporation of cinnamon essential oil introduced stronger antibacterial activity and was associated with favorable fibroblast responses. The study provides one of the clearest demonstrations that oil-palm-derived nanocellulose can progress beyond conventional composite applications toward biologically relevant scaffold systems [16].

An additional development extended OPEFB-derived cellulose toward hard-tissue applications. Zulkifli et al. (2025) [17] fabricated water-stable soy protein isolate/carboxymethyl cellulose scaffolds in which CMC was sourced from OPEFB. The resulting porous structures were assessed for characteristics relevant to bone tissue engineering and supported attachment and proliferation of human fetal osteoblast cells. The work also demonstrated a critical design trade-off: scaffold composition and porosity can improve aspects of cellular accessibility and biological function while simultaneously influencing Young's modulus and structural performance. This is precisely the kind of trade-off that becomes important when the ultimate objective shifts from in vitro compatibility to functional tissue regeneration [17]. These developments create an important research opportunity but also a risk of conceptual overstatement. The broader nanocellulose literature now includes numerous studies on wound dressings, skin substitutes, bone scaffolds, cartilage constructs, bioinks, vascular materials, antimicrobial systems, and regenerative platforms. However, evidence obtained from bacterial nanocellulose, wood-derived CNF, tunicate cellulose, or other lignocellulosic sources cannot automatically be presented as evidence that OPEFB-derived nanocellulose performs identically. The source, purification, functionalization, and scaffold manufacturing process matter. Accordingly, a rigorous review must distinguish direct OPEFB evidence from transferable design knowledge obtained from the wider nanocellulose literature [9-19].

A second conceptual challenge concerns the meaning of regeneration itself. Tissue engineering commonly assesses cell viability, proliferation, differentiation, mineralization, collagen formation, wound closure, or tissue ingrowth. These are important outcomes, but successful regenerative medicine ultimately aims to restore tissue performance. Regenerated bone must eventually tolerate mechanical loading; repaired skin must restore barrier function, elasticity, integrity, and resistance to recurrent injury. For musculoskeletal tissues in particular, rehabilitation is not simply something that happens after biological repair has ended. Mechanical stimuli can regulate cellular signalling, inflammatory behavior, angiogenesis, extracellular matrix organization, osteogenesis, and tissue remodeling throughout healing [20, 21, 22, 23]. This insight underlies the emerging field of regenerative rehabilitation, which seeks to integrate regenerative interventions with rehabilitation science so that biological repair translates into functional recovery. Mechanobiology becomes a theoretical bridge between the two domains because cells sense forces, substrate stiffness, strain, shear, geometry, and loading history and convert them into biochemical signals. Contemporary mechanobiomaterial research increasingly treats mechanical properties not as passive engineering specifications but as biological instructions that can shape regenerative outcomes [24, 25].

The central purpose of this qualitative literature review is therefore to evaluate oil-palm-derived cellulose scaffolds through a biomass-to-function translational lens. Four questions guide the analysis. First, how can oil palm biomass be transformed into cellulose and nanocellulose scaffolds with physicochemical and biological characteristics relevant to regenerative medicine? Second, what contemporary evidence supports their potential in wound/skin regeneration and bone tissue engineering? Third, how can mechanobiology conceptually connect scaffold-medi-

ated tissue regeneration with functional recovery and regenerative rehabilitation? Fourth, which biosafety, manufacturing, regulatory, and evidentiary barriers must be addressed before these materials can progress toward clinical relevance? By answering these questions, this review shifts the discussion from whether oil palm biomass can produce nanocellulose toward the more demanding question of what would be required for such materials to become truly regenerative.

Literature Review: Conceptual and Theoretical Foundations

From Circular Biomass Utilization to Regenerative Biomaterials

Circular bioeconomy thinking provides the first conceptual foundation for this topic. Agricultural biomass acquires greater value when processing strategies retain or enhance functionality rather than simply redirect material flows. OPEFB has already been examined as feedstock for fuels, chemicals, fibers, composites, cellulose, nanocellulose, and hydrogels. Reviews published since 2020 have emphasized its abundance, cellulose potential, and suitability for higher-value conversion, although industrial scalability, pretreatment costs, chemical consumption, supply-chain integration, and consistent feedstock quality remain relevant constraints [26, 2, 1]. Biomedical valorization, however, introduces requirements substantially more stringent than those applicable to packaging, adsorbents, structural composites, or conventional industrial materials. Residual lignin, hemicellulose, extractives, microorganisms, endotoxin-like contaminants, processing chemicals, crosslinkers, and other impurities that may be tolerable in an engineering material can become unacceptable when the product contacts wounds, cells, tissues, or blood. Consequently, sustainable extraction must be reconciled with biomedical-grade purification. The environmental desirability of mild or low-chemical processing is valuable only if it yields reproducible materials whose biological risks are understood and controlled [9].

The term regenerative biomaterial is itself useful in distinguishing advanced biomedical function from passive material substitution. Cao and Ding (2022) [3] describe the evolution of biomaterials from relatively inert supports toward materials designed to elicit or guide biological processes. In this framework, regenerative effectiveness emerges from interactions among material properties, cells, host tissue, immune responses, degradation, and physiological conditions. Such a perspective is particularly appropriate for nanocellulose because its hydroxyl-rich surface, fibrillar morphology, water retention, rheology, and modifiability allow its role to extend from structural reinforcement toward more active regulation of the cellular microenvironment.

Nanocellulose Forms and Scaffold Architecture

The differences among CNC, CNF, and BNC have implications for scaffold design. CNCs possess highly crystalline rod-like structures and are frequently used as reinforcing phases or rheological modifiers. CNFs contain crystalline and amorphous domains and form entangled networks with high aspect ratios; they are particularly suitable for hydrogels, aerogels, films, and composite networks. BNC is synthesized extracellularly by microorganisms and commonly presents a highly hydrated three-dimensional nanofibrillar network with high purity when appropriately processed. These distinctions affect rheology, mechanical reinforcement, water management, pore formation, printing behavior, functionalization, and cellular interactions [5, 6, 27]. Hydrogels and aerogels are especially relevant because tissue-engineering scaffolds require interconnected three-dimensional environments. Nanocellulose can reinforce hydrogel networks while preserving high water content, thereby addressing one of the traditional limitations of very soft hydrogels: poor mechanical integrity. Porous nanocellulose foams and aerogels also allow substantial control over pore architecture and surface chemistry, both of which influence cell attachment, diffusion, and three-dimensional culture performance [28]. Nevertheless, increasing crosslinking or reinforcement to improve mechanics may reduce pore accessibility, swelling, diffusion, or degradation. Scaffold design therefore requires optimization rather than maximization of individual properties [6, 28-31]. Additive manufacturing offers a further route toward architecture control. Kuhnt and Camarero-Espinosa [10] emphasized that nanocellulose in additive manufacturing can do more than act as a filler: nanoscale topographical and mechanical cues can be designed to influence cellular function. Patel et al. [32] demonstrated printable CNC-containing hydrogels, while Maturavongsadit et al. [33] developed cell-laden nanocellulose/chitosan bioinks in which CNC incorporation improved rheology and mechanical characteristics and supported osteogenic differentiation. More recent reviews show continuing expansion of nanocellulose bioinks for bone, cartilage, skin, muscle, and tissue modeling [25, 34].

Cell–Scaffold Interaction as the Core of Regenerative Function

The most important transition from biomaterial to regenerative biomaterial occurs at the cell–material interface. When a scaffold is placed in a biological environment, proteins adsorb to its surface before most cells directly interact with the underlying material. Surface chemistry, charge, hydrophilicity, roughness, nanoscale topography, stiffness, and ligand availability subsequently influence adhesion complexes, cytoskeletal organization, spreading, migration, survival, and signalling. The scaffold therefore operates simultaneously as a physical structure and a biochemical/mechanical information environment [11, 12]. Porosity illustrates the multidimensional nature of this relationship. High porosity can enhance fluid transport, oxygen and nutrient diffusion, surface availability, cell infiltration, and tissue ingrowth. Yet very high porosity often reduces stiffness and load-bearing performance. Pore size and connectivity also need to match tissue-specific requirements; an architecture favorable for a hydrated wound dressing is not necessarily appropriate for mineralized bone regeneration. Sreedharan et al. [14] therefore emphasize hybrid scaffold strategies in which nanocellulose is combined with collagen, gelatin, minerals, or other components to overcome the limitations of single-material systems.

Biomimicry must also be interpreted cautiously. Nanofibrillar cellulose networks can resemble certain structural aspects of extracellular matrix, but morphological resemblance does not mean biological equivalence. Native extracellular matrix contains collagen, glycosaminoglycans, adhesion proteins, enzymes, bound growth factors, tissue-specific mechanical gradients, and dynamic remodeling signals. Nanocellulose often requires functionalization or combination with biologically active components to achieve comparable cell-instructive effects. This is why modern scaffold strategies increasingly use hybridization rather than relying on cellulose alone 2023 [14, 35].

Tissue-Specific Regenerative Requirements

Skin and bone illustrate two markedly different regenerative contexts. Wound-healing materials must manage fluid, maintain an appropriately moist environment, permit gas exchange, reduce trauma during dressing changes, limit microbial colonization, conform to irregular surfaces, and support fibroblast, keratinocyte, endothelial, immune, and extracellular-matrix responses. Nanocellulose is attractive because of water retention and its three-dimensional fibrillar network, but antimicrobial functionality usually requires modification because cellulose itself should not automatically be regarded as strongly antimicrobial [36, 37, 38]. Bone presents greater mechanical and mineralization requirements. Bone scaffolds must facilitate cell attachment, migration, osteogenic differentiation, vascularization, extracellular matrix formation, calcium-phosphate mineralization, and eventual mechanical integration. Porosity is essential for tissue ingrowth, but insufficient strength can limit load-bearing applications. Composite strategies incorporating hydroxyapatite, proteins, chitosan, or bioactive phases have therefore become prominent [3, 35, 39]. This tissue-specificity undermines the idea of a universal nanocellulose scaffold. The optimal formulation for skin may emphasize hydration, flexibility, antimicrobial functionality, and controlled adhesion. A bone scaffold may require mineralization, anisotropy, compressive performance, osteoconductive chemistry, and gradual load transfer. The regenerative potential of oil-palm-derived nanocellulose should therefore be evaluated through application-specific design criteria, rather than general claims of biocompatibility.

Mechanobiology and Regenerative Rehabilitation

Mechanobiology provides the principal theoretical bridge from scaffold architecture to rehabilitation. Cells respond to substrate stiffness, cyclic deformation, compression, tension, shear, fluid flow, and matrix architecture through mechanosensitive structures and signalling pathways. These signals can influence proliferation, migration, inflammatory phenotype, extracellular matrix production, and lineage commitment. In bone, mechanical stimuli are integral to adaptation and remodeling; in connective tissue and wound healing, mechanical tension influences fibroblast behavior and matrix organization [24, 25, 40]. The field of regenerative rehabilitation extends this concept to therapeutic intervention. Mechanical loading through exercise or other rehabilitation modalities can potentially be timed and dosed to complement regenerative therapies. McKay et al. [20] reviewed mechanobiology-based rehabilitation after orthobiologic interventions and emphasized that different mechanical modalities may be appropriate across different healing phases. Seo and Mooney [21] similarly described mechanotherapy as a route for deliberately applying physical forces to influence regeneration. More recent regenerative-rehabilitation literature has emphasized the mechanosensitivity of macrophages, fibroblasts, mesenchymal stromal cells, and other cell populations involved in healing [22, 23].

This does not establish that oil-palm-derived nanocellulose scaffolds have already been integrated successfully with clinical rehabilitation. Rather, it provides a conceptual research direction. If a future OPEFB-derived scaffold is implanted for musculoskeletal regeneration, its stiffness, degradation, tissue integration, and changing mechanical environment may influence when loading can safely begin and what loading magnitude is biologically beneficial. The scaffold and rehabilitation protocol would then need to be designed as coupled components rather than sequentially independent interventions.

Method

This study employed a qualitative literature review, specifically an interpretive and integrative form of narrative synthesis. This design was selected because the research problem spans heterogeneous literatures in biomass valorization, materials science, tissue engineering, mechanobiology, and rehabilitation that cannot be meaningfully reduced to a single effect estimate. Narrative and integrative reviews are particularly useful when the objective is to interpret a broad and conceptually diverse evidence base, identify tensions, and develop new explanatory connections rather than answer a narrowly specified intervention question [41]. Accordingly, the purpose was not to determine a pooled treatment effect, calculate prevalence, rank interventions statistically, or produce a comprehensive inventory of every publication on nanocellulose; instead, the review sought to connect bodies of scholarship that are usually treated separately: oil palm biomass valorization, cellulose chemistry, nanocellulose engineering, tissue engineering, wound healing, bone regeneration, mechanobiology, regenerative rehabilitation, and biomaterial translation.

The methodological design was intentionally distinct from a systematic literature review. No PRISMA flow diagram was produced, no claim is made that every record matching a predetermined search string was captured, and no fixed numerical inclusion/exclusion process or meta-analysis was conducted. Instead, transparency was pursued by stating the conceptual scope, publication window, principal search concepts, evidence-maturity categories, and interpretive logic used to connect the literature. This approach is consistent with the flexibility of narrative knowledge synthesis when the principal objective is interpretation and theory building rather than exhaustive retrieval or pooled estimation [41]. Literature exploration was conducted iteratively and purposively, with emphasis on peer-reviewed studies published from 2020 through August 2026. Searches focused on combinations of terms including oil palm biomass, oil palm empty fruit bunch, OPEFB, cellulose nanofiber, nanocellulose, cellulose nanocrystal, carboxymethyl cellulose, bioaerogel, hydrogel, scaffold, tissue engineering, wound healing, skin regeneration, bone tissue engineering, osteoblast, fibroblast, mechanobiology, mechanotransduction, mechanotherapy, regenerative rehabilitation, biosafety, and clinical translation. Priority was given to articles indexed or published through established scholarly platforms and reputable peer-reviewed journals, and citation chaining was used to identify conceptually important studies that connected otherwise separate disciplinary literatures. This iterative strategy was used to improve conceptual coverage while preserving the non-systematic, interpretive character of the qualitative review [41].

Literature selection followed conceptual relevance rather than statistical exhaustiveness. Direct studies involving OPEFB-derived cellulose or nanocellulose were prioritized because they establish source-specific evidence. Broader nanocellulose studies were then used to identify transferable design principles, such as biomineralization, hybridization, 3D printing, anisotropic architecture, antimicrobial functionalization, scaffold mechanics, and

mechanobiological conditioning. This distinction was essential because BNC, wood-derived CNF, tunicate nanocellulose, and OPEFB-derived materials cannot be treated as biologically interchangeable. Thematic coding developed around six domains: (1) biomass-to-biomaterial conversion; (2) structure–property–biofunction relationships; (3) cell–scaffold interaction; (4) wound and skin regeneration; (5) bone tissue engineering; and (6) mechanobiology, regenerative rehabilitation, and translational readiness. Evidence was interpreted according to its stage of maturity, distinguishing material characterization from in vitro cytocompatibility, tissue-specific cell function, animal evidence, clinical evidence, and functional rehabilitation outcomes.

This evidence-maturity distinction is important for avoiding a common problem in emerging biomaterial literature. Demonstrating high porosity or favorable water absorption does not establish tissue regeneration; demonstrating >70% cell viability does not establish tissue-specific functional integration; and demonstrating tissue formation in an animal model does not establish human clinical effectiveness. The analysis therefore treated increasingly advanced outcomes as progressively stronger levels of translational evidence rather than as equivalent observations. The qualitative nature of the review inevitably introduces limitations. Selection and interpretation depend partly on conceptual judgment, and heterogeneous scaffold formulations preclude straightforward comparison. Furthermore, direct oil-palm-specific biomedical evidence is substantially smaller than the general nanocellulose literature. To manage this limitation, the discussion consistently differentiates between results demonstrated in OPEFB-derived systems and principles inferred from related nanocellulose systems.

Results: Contemporary Thematic Findings

Theme 1: Oil Palm Biomass Is Progressing from Residual Feedstock to Advanced Biomaterial

The first thematic finding is a clear progression in the scientific narrative surrounding OPEFB. Earlier valorization pathways concentrated largely on energy, fiber products, bulk composites, and biochemical conversion. Since 2020, however, literature has increasingly discussed nanocellulose extraction, hydrogel production, and high-functionality materials. Padzil et al. [26] explicitly identified OPEFB as a viable feedstock for nanocellulose hydrogel development, while Lim et al. [1] placed oil-palm-derived nanocellulose within a broader sustainable-materials and circular-economy context.

The significance of this transition lies in the change in functional expectations. Producing cellulose from agricultural residue demonstrates resource recovery, whereas producing nanocellulose establishes nanoscale material engineering and introduces additional requirements for morphology and surface control. Creating a scaffold then requires deliberate control over three-dimensional architecture, and a regenerative scaffold must further support tissue-relevant biological processes. Each successive stage therefore adds a higher performance threshold and a new class of technical, biological, and translational failure risks [6, 8, 43]. The OPEFB study by Yahya et al. [16] is particularly significant in this progression. CNF derived from oil palm waste was transformessd into bioaerogels with very high porosity. Chitosan modification enhanced mechanical characteristics and reduced excessive water uptake, whereas cinnamon essential oil imparted stronger antibacterial activity and supported favorable fibroblast responses. This provides direct evidence that the biomass-to-regenerative-material pathway is technically plausible, even though the experiment remains far from clinical validation.

Figure 1 summarizes the conceptual shift that structures the entire review. Rather than treating nanocellulose production as the endpoint of biomass valorization, the figure positions material production as the first segment of a longer translational pathway toward tissue and functional outcomes.

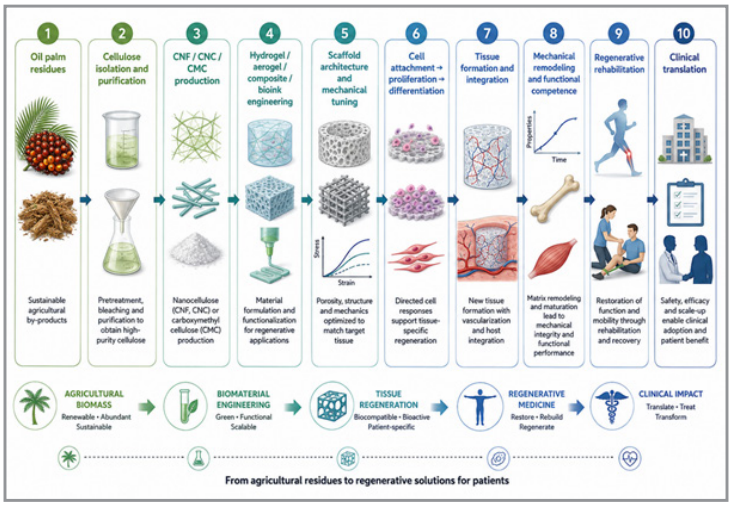

Figure 1: Biomass-to-Function Translational Value Chain

Figure 1 emphasizes that the material origin alone does not establish regenerative value. The pathway contains multiple translational gates: purity, reproducibility, scaffold fabrication, cellular compatibility, tissue-specific function, integration, mechanics, rehabilitation response, and clinical safety.

A failure at any one of these stages can prevent a sustainable biomass-derived material from becoming a clinically meaningful regenerative technology.

Theme 2: Scaffold Function Emerges from Structure–Property–Biofunction Relationships

A second consistent finding is that nanocellulose scaffold performance cannot be reduced to a single favorable material property.

Porosity, hydrophilicity, stiffness, degradation, surface chemistry, and biological modification interact. High water retention is advantageous in wound care but excessive swelling may weaken structural integrity. High porosity supports diffusion and cellular access but can reduce modulus. Strong chemical crosslinking may improve dimensional stability while introducing potentially undesirable residues or limiting degradation [29-31]. Hybridization is consequently a dominant strategy. Nanocellulose can reinforce otherwise soft biopolymers, while proteins or bioactive polymers can provide cellular interaction motifs that cellulose lacks. Chitosan adds antimicrobial potential and changes mechanics; gelatin and collagen provide biologically recognizable components; hydroxyapatite introduces mineral cues for bone; proteins such as soy protein isolate can contribute complementary structure and biological interaction. Sreedharan et al. [14] describe nanocellulose hybrids as particularly important in skin and bone tissue engineering because the combination can overcome weaknesses inherent in individual materials. The bone-scaffold study by Zulkifli et al.[17] illustrates the central design dilemma. Increasing porosity can facilitate cell penetration and fluid exchange but may lower stiffness. A successful scaffold therefore requires a tissue-specific performance window rather than maximal porosity or maximal modulus. Bone engineering amplifies this tension because the scaffold must permit biological invasion while retaining sufficient mechanical stability to protect regenerating tissue.

Figure 2 demonstrates how physical scaffold parameters become biological signals rather than merely engineering specifications. It also makes explicit that upstream decisions concerning source, fabrication, and formulation propagate through fluid and cellular interactions to shape tissue-level and functional outcomes.

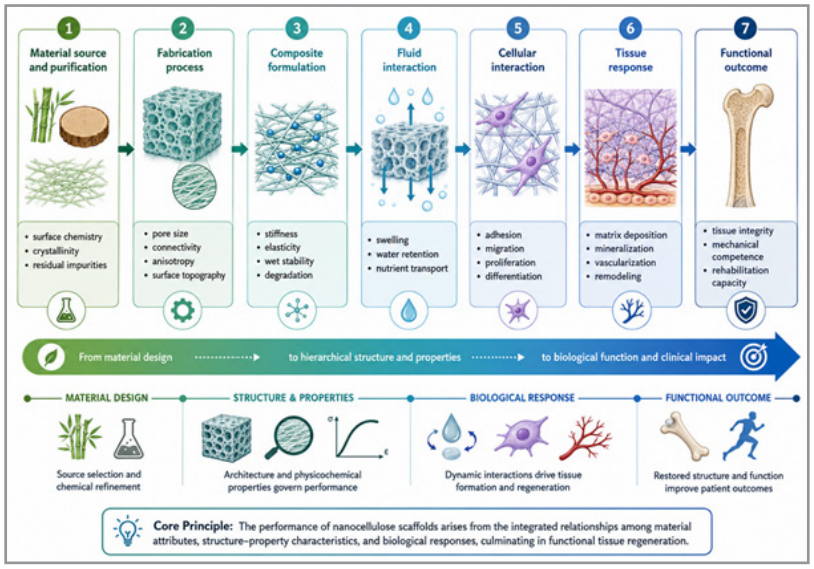

Figure 2: Structure–Property–Biofunction Framework for Nanocellulose Scaffolds

The framework illustrates why scaffold optimization is inherently multidimensional. The same processing decision can produce beneficial and adverse downstream effects. Increased crosslink density, for example, may improve wet-state strength but reduce pore dynamics or alter degradation; increased mineral loading may improve osteoconductivity yet impair printability. Translational scaffold engineering therefore involves balancing competing requirements rather than independently maximizing material properties.

Theme 3: Cell–Scaffold Interaction Determines Whether a Material Becomes Regenerative

A third theme is the centrality of biological interaction. Many nanocellulose studies report cytocompatibility, but advanced tissue engineering increasingly examines cell morphology, attachment, proliferation, differentiation, matrix deposition, and phenotype-specific markers. Maturavongsadit et al. [33], for example, reported that CNC-containing chitosan bioinks could support viable 3D-bioprinted pre-osteoblasts and that CNC incorporation was associated with improved osteogenic indicators, including alkaline phosphatase activity, calcium mineralization, and extracellular matrix formation. Material architecture also influences these interactions. Jiao et al. [44] demonstrated that anisotropic nanocellulose scaffolds reinforced through biomineralization could achieve substantial modulus increases and provide environments favorable to mesenchymal-stem-cell growth and directed differentiation. This suggests that nanoscale fiber orientation and mechanical anisotropy can be treated as cell-instructive design variables, not simply as structural outcomes of manufacturing.

Biomineralized bacterial nanocellulose provides complementary evidence. Cañas-Gutiérrez et al.[45] developed three-dimensional BNC scaffolds containing calcium-phosphate phases and investigated stem-cell differentiation. Their findings illustrate how cellulose surfaces can be transformed from relatively biologically neutral fibrillar networks into mineralized environments that better reproduce aspects of bone composition and osteogenic signalling. Similarly, Korkeamäki et al. [46] incorporated nano-hydroxyapatite into porous CNF scaffolds to improve osteoconductive characteristics while examining osteoblast-like cell responses.

These findings are relevant to OPEFB even though they do not constitute direct OPEFB evidence. They define a research agenda: future oil-palm-derived scaffolds should progress from fibroblast or osteoblast viability toward cell adhesion mechanisms, phenotype-specific differentiation, immune-cell interaction, vascularization, matrix organization, and dynamic mechanobiological testing.

Theme 4: Skin and Wound Healing Are the Most Immediately Plausible Soft-Tissue Applications

Nanocellulose is particularly compatible with wound-dressing design because wound care benefits from high hydration, conformability, porous mass transfer, and the possibility of incorporating antibacterial or bioactive agents. Contemporary reviews consistently identify BNC, CNF, and CNC systems as promising wound materials, while also emphasizing the need for modification to provide active antimicrobial, anti-inflammatory, antioxidant, angiogenic, sensing, or drug-delivery functions [36-38, 47-49]. Recent synthesis further indicates that the clinical promise of cellulose-based nanofibers depends on balancing moisture management, mechanical integrity, infection control, and tissue compatibility rather than optimizing any one attribute in isolation [14-49]. The wound-healing process involves overlapping phases of hemostasis, inflammation, proliferation, and remodeling. A useful dressing must therefore manage changing biological requirements rather than merely cover the wound. During early stages, infection control and exudate management can be critical. During proliferative phases, fibroblast migration, endothelial activity, granulation tissue formation, extracellular matrix deposition, and re-epithelialization become prominent. Later remodeling determines scar structure and mechanical integrity.

Recent nanocellulose systems illustrate increasingly active approaches. Sun et al. [49] developed BNC-based dressings incorporating polydopamine and copper sulfide nanoparticles. Under near-infrared stimulation, the composite provided photothermal/photodynamic antibacterial effects and copper-ion-mediated angiogenic support, with in vivo evidence of accelerated closure of infected full-thickness wounds. Chamchangi et al. [50] similarly investigated BNC-containing nanohydrogels incorporating bitter almond oil nanoemulsions and reported favorable in vitro and in vivo wound-healing characteristics. These systems demonstrate how nanocellulose can serve as a platform for multifunctional wound therapy rather than as an inert covering. The direct OPEFB evidence is more limited but strategically important. Yahya et al. [16] demonstrated antibacterial functionality and fibroblast compatibility in OPEFB-derived CNF bioaerogels. This supports the plausibility of wound-related applications, but it should not be interpreted as evidence that the material already restores complex skin structure in vivo. Important unanswered questions include keratinocyte migration, re-epithelialization, angiogenesis, immune modulation, collagen architecture, scar quality, chronic-wound performance, diabetic wounds, and burn healing.

Figure 3 positions scaffold functions against the biological phases of wound healing and helps distinguish supportive material functions from genuinely regenerative outcomes. This continuum is important because the performance requirements of a dressing change over time, while moisture balance, biosafety, structural integrity, and controlled degradation remain cross-cutting requirements.

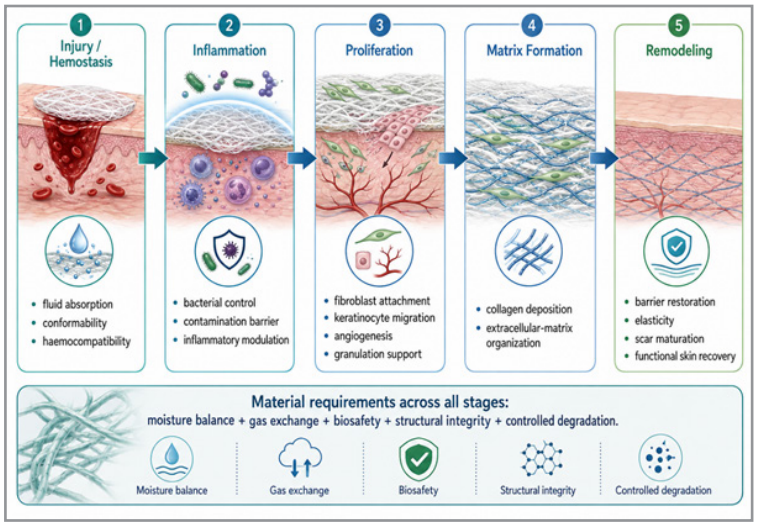

Figure 3: Nanocellulose Scaffold Functions Across the Wound-Healing Continuum

Figure 3 highlights a key distinction for future oil-palm nanocellulose research. Fibroblast proliferation represents one component of wound repair but cannot serve as a surrogate for the entire regenerative process. Advanced studies should evaluate vascular, epidermal, immune, extracellular-matrix, mechanical, and functional endpoints if the field is to progress from wound-dressing materials toward true skin-regenerative scaffolds.

Theme 5: Bone Tissue Engineering Provides a More Demanding Test of Regenerative Capability

Bone tissue engineering presents a stronger challenge to cellulose-based scaffolds because the tissue is simultaneously biological, mineralized, vascularized, and mechanically loaded. Nanocellulose can provide a fibrillar network and reinforcement, but it usually requires additional components or functionalization to achieve osteoconductivity and appropriate mechanics. Reviews of nanocrystalline cellulose, bacterial cellulose, and cellulose composites consistently identify hydroxyapatite mineralization, composite reinforcement, controlled porosity, and osteogenic differentiation as key strategies [5, 35, 39, 51]. Cao et al. [3] developed oxidized bacterial-cellulose/chitosan/nano-hydroxyapatite composite scaffolds. Their cell experiments indicated compatibility and increased proliferation of MC3T3-E1 cells, while rat skull-defect experiments showed enhanced bone formation relative to comparison formulations. The result is significant because it demonstrates progression from material characterization through in vitro cell testing to in vivo bone regeneration within a nanocellulose-containing system. More recent work with bacterial-nanocellulose/chitosan hydrogel scaffolds has reinforced

the importance of examining biodegradation and cytocompatibility together, because a scaffold must retain sufficient integrity during early repair while permitting progressive replacement by newly formed tissue [52].

Biomineralization strategies further address the mismatch between cellulose and mineralized bone. Cañas-Gutiérrez et al. [44] demonstrated calcium-phosphate formation within microporous BNC scaffolds, and Jiao et al. [43] used in situ biomineralization to strengthen anisotropic nanocellulose matrices and guide mesenchymal-stem-cell responses. Korkeamäki et al. [45] similarly showed that nano-hydroxyapatite incorporation changes the microarchitecture and biological functionality of CNF scaffolds. Together, these studies suggest that future OPEFB-derived bone scaffolds are likely to require hybridization rather than relying on purified cellulose alone. Three-dimensional bioprinting offers another path toward tissue-specific architecture. Lin et al. (2023) reviewed nanocellulose and cellulose-derivative bioinks for bone and cartilage engineering and emphasized printability, biodegradability, mechanics, and cell compatibility as interdependent requirements. Walters-Shumka et al. [34] subsequently highlighted continuing development of nanocellulose-containing bioinks for bone, cartilage, skin, and muscle tissue models. Within this broader context, the OPEFB-derived CMC scaffold reported by Zulkifli et al. (2025) [17] represents a strategically important source-specific development. Osteoblast attachment and proliferation establish basic biological feasibility, while mineral deposition and scaffold stability provide preliminary evidence relevant to bone. Yet the material remains far from demonstrating regeneration of critical-size defects under physiological loading. Future studies require osteogenic differentiation markers, vascularization, in vivo defect models, degradation analysis, inflammatory assessment, new-bone quantification, and biomechanical testing.

Theme 6: Mechanobiology Is the Missing Bridge Between Tissue Formation and Functional Recovery

One of the strongest findings of this review is that regenerative-material studies and rehabilitation studies often stop at opposite sides of the same biological process. Biomaterials research may end with tissue formation, whereas rehabilitation research begins with the progressive restoration of movement, loading, or function. Mechanobiology shows that this boundary is artificial because forces influence tissue behavior throughout healing. Entezari et al. [40] demonstrated a scaffold-design strategy specifically intended to incorporate mechanotransduction principles into bone tissue engineering. Their modular system protected mechanically weak bioactive scaffolds while permitting osteoinductive strain levels. This work illustrates a crucial idea for nanocellulose: mechanically weak or highly hydrated scaffolds need not necessarily be excluded from load-associated tissues if surrounding architecture can regulate the strain transferred to the regenerating construct. Sheehy et al. (2021) further demonstrated how mechanobiology can inform regenerative intervention design by using knowledge of mechanically regulated placental growth factor to construct a scaffold-delivery strategy promoting angiogenesis and bone healing. The study illustrates a broader principle: information derived from mechanical biology can be embedded prospectively into biomaterial design rather than applied only after scaffold implantation. Regenerative rehabilitation extends this logic clinically. Jacho and Yildirim-Ayan (2024) [22] emphasize that macrophages, fibroblasts, and mesenchymal stem cells exhibit phase-dependent mechanosensitivity. Deng et al. (2024) [23] frame regenerative rehabilitation as an interdisciplinary convergence intended to maximize functional outcomes, while Garg et al. (2025), discussing volumetric muscle loss, show that integration of scaffolds and rehabilitation remains promising but clinically immature. Importantly, premature or excessive loading can damage regenerating tissue or a scaffold–tissue interface, whereas insufficient loading may fail to provide signals needed for organized remodeling.

Figure 4 shows the bidirectional relationship between scaffold mechanics, cells, tissue remodeling, and rehabilitation. The feedback loop emphasizes that rehabilitation loading can alter the evolving tissue-scaffold environment, which in turn changes subsequent mechanosensing and load tolerance.

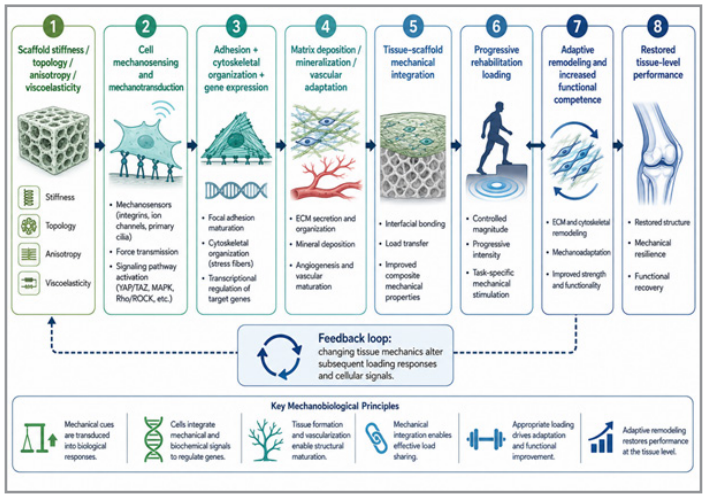

Figure 4: The Mechanobiological Bridge from Scaffold to Regenerative Rehabilitation

Figure 4 shifts rehabilitation from the conceptual status of a post-regeneration activity to that of a potential biological regulator of regeneration. For future OPEFB-based musculoskeletal scaffolds, this means that wet-state modulus, strain transfer, degradation kinetics, and integration should eventually be evaluated under dynamic loading rather than exclusively under static culture conditions.

Theme 7: Translation Is Constrained by a Multi-Dimensional Readiness Gap

A final theme concerns the distance between encouraging laboratory results and clinically usable regenerative products. Biomedical nanocellulose literature frequently cites biocompatibility, renewability, and sustainability as advantages, but Li et al. (2024) [9] caution that nanoscale cellulose should not automatically inherit a universal safety designation from bulk cellulose. Residual endogenous components, external contaminants, production chemicals, source-dependent variability, surface modification, particle dimensions, and route of exposure all affect biosafety assessment. Sterilization presents another problem. A scaffold must be manufactured aseptically or sterilized without losing architecture, chemistry, mechanical properties, or biological function. De Wit et al. (2023) illustrated the relevance of sterilization methodology in scaffold-based tissue engineering, while Janmohammadi et al. [35] explicitly identified sterilization and regulatory barriers among challenges to clinical translation of cellulose-based bone scaffolds.

Manufacturing reproducibility is particularly important for agricultural feedstocks. Oil-palm biomass composition can vary with biological source, age, processing, storage, and pretreatment. Biomedical manufacturing cannot rely on a vague specification of "OPEFB-derived nanocellulose"; it requires quantitative specifications for cellulose purity, fiber dimensions, crystallinity, surface charge, residual chemicals, microbiological burden, mechanical performance, batch variability, and scaffold architecture. Clinical translation literature demonstrates that these challenges are not unique to cellulose. Pedersen et al. (2022) found relatively few biodegradable polyurethane scaffold systems had achieved routine clinical application despite extensive preclinical development. Golebiowska et al. (2024) and Capella-Monsonís et al. (2024) similarly emphasize manufacturing, preservation, regulatory pathways, implantation, cost, and clinically relevant validation as recurring bottlenecks for regenerative biomaterials. Regulation becomes more complicated as materials acquire additional functions. A simple wound-contact material may face one regulatory route, while a cell-laden bioink, growth-factor-containing scaffold, or tissue-engineered construct may be classified differently. Jurczak et al. (2025) highlight how increasingly complex biomaterial-based medical devices must integrate safety and manufacturability considerations early in development rather than treating regulatory comfpliance as a final-stage administrative task.

Discussion and Analysis

Answering RQ1: How Can Oil Palm Biomass Become a Regenerative Biomaterial?

The literature indicates that the transformation requires at least three distinct transitions. The first is biomass-to-cellulose, involving pretreatment, removal of lignin and hemicellulose, purification, and control of chemical residues. The second is cellulose-to-engineered scaffold, in which nanoscale morphology, crosslinking, porosity, composites, and three-dimensional fabrication determine material functionality. The third, and most demanding, is scaffold-to-regenerative microenvironment, where the construct must influence cells and host tissues in ways consistent with tissue repair. This distinction clarifies why successful nanocellulose extraction should not be treated as equivalent to successful regenerative biomaterial development. OPEFB can be an economically and environmentally attractive cellulose source, but medical utility emerges only after stringent purification, reproducible processing, application-specific scaffold engineering, and biological validation. The implied causal sequence runs from feedstock quality through extraction and purification, nanoscale properties, scaffold architecture, cell interaction, and tissue response to functional integration. Treating this sequence as a set of linked translational gates helps prevent strong downstream claims from being inferred from evidence that exists only at the material-characterization stage. The OPEFB-specific literature currently supports the first several links much more strongly than the last. Padzil et al. (2020) [26] and Lim et al. (2022) establish the material potential; Yahya et al. (2023) [16] extend this toward fibroblast-compatible antibacterial scaffolds; and Zulkifli et al. (2025) [17] extend it toward osteoblast-interactive bone-scaffold systems. Evidence of long-term tissue integration and restored function remains largely absent.

Answering RQ2: How Strong Is the Evidence for Skin and Bone Regeneration?

For wound-related applications, the evidence is promising because OPEFB CNF bioaerogels already demonstrate several characteristics aligned with wound materials: high porosity, water interaction, antibacterial functionalization, and fibroblast compatibility. Yet skin regeneration is biologically more complex than fibroblast proliferation. Future studies must establish whether the scaffold supports keratinocytes, endothelial cells, immune regulation, re-epithelialization, angiogenesis, collagen organization, and restoration of barrier function. The broader nanocellulose literature provides useful design possibilities. Yang et al. [37], Hou et al.[38], Meng et al. [36], Pasaribu et al. [47], and Razia and Hastuti [48] collectively demonstrate the rapid evolution from passive BNC or nanocellulose dressings toward multifunctional systems. Sun et al. [49] and Chamchangi et al. [50] illustrate how active therapeutic components can add antibacterial, angiogenic, or other biological functions. The implication is not that these effects can be attributed automatically to OPEFB-derived CNF; rather, they identify testable modifications for future OPEFB scaffolds.

Bone evidence is at an earlier source-specific stage but may have greater long-term regenerative significance. Zulkifli et al. (2025) [17] provide direct OPEFB-CMC evidence relevant to osteoblast behavior. The broader literature demonstrates that cellulose scaffolds can be mineralized, reinforced, made anisotropic, bioprinted, and combined with hydroxyapatite to support osteogenic processes [35, 44, 45, 46]. These studies supply a design toolbox for translating OPEFB cellulose toward bone applications. The evidence nevertheless remains asymmetrical. The field has substantial evidence that nanocellulose can be engineered for bone-related biological functions, but much less evidence that oil-palm-derived nanocellulose specifically reproduces those functions in vivo. This distinction should remain explicit in any claim of novelty or clinical relevance.

Tissue-Specific Design Means That "Nanocellulose Scaffold" Is Too Broad a Category

The qualitative synthesis strongly suggests that future research should abandon generic claims that a nanocellulose scaffold is "suitable for tissue engineering." Suitability is tissue specific. Skin, bone, cartilage, nerve, muscle, and cardiovascular tissues

impose different architecture, mechanical, degradation, and biological requirements. For wound applications, flexible and highly hydrated systems may be desirable. High water retention helps maintain a moist wound environment, and an interconnected porous network can support mass transfer. However, the material must remain sufficiently intact during handling and removal. Antibacterial enhancement should avoid cytotoxic concentrations of metals, essential oils, or antimicrobial compounds. For bone, the challenge is almost the opposite. Excessive softness may prevent stable tissue formation under load. Mineralization, compressive properties, anisotropy, vascularization, osteogenesis, and controlled degradation become major priorities. The trade-off observed in OPEFB-derived CMC scaffolds between increasing porosity and reduced modulus is therefore not merely an engineering inconvenience; it is a fundamental translational problem. This tissue-specific perspective also clarifies the value of 3D printing and hybrid formulations. Nanocellulose may function as a rheological modifier, structural network, reinforcement phase, or bioactive platform, but additional polymers and minerals can tailor the construct for different tissues. Lin et al. [25] and Walters-Shumka et al. [34] indicate that this modularity is one reason nanocellulose remains attractive for advanced biofabrication.

Answering RQ3: Functional Recovery Requires a Mechanobiological Extension of Scaffold Research

The most distinctive contribution of this review is the proposition that the future of oil-palm-derived regenerative biomaterials should not terminate at histological evidence of regeneration. Tissue quality must eventually be assessed through function, because restoration of structure without restoration of load tolerance, barrier performance, mobility, or other tissue-specific capabilities remains an incomplete regenerative outcome [22, 23]. Bone provides the clearest example. An engineered construct can contain new mineralized tissue while still having poor load transfer, inadequate architecture, insufficient fatigue resistance, or weak integration with adjacent bone. A wound may close while leaving fragile, fibrotic, poorly vascularized, or mechanically abnormal skin. Functional regeneration therefore requires outcome measures beyond cell survival and tissue quantity. Mechanobiology provides a framework for this transition. Lin et al. (2024) [25] describe mechanobiomaterials as systems in which mechanics–geometry–biofunction relationships are deliberately engineered. This idea complements conventional biomaterial design: scaffold stiffness, geometry, architecture, and deformation become biological variables. Mechanical conditioning can influence cytoskeletal organization, mechanosensitive pathways, differentiation, matrix production, inflammatory phenotypes, and remodeling.

The implication for oil-palm-derived scaffolds is substantial. Future bone constructs could be evaluated under dynamic compression or loading regimes that approximate rehabilitation rather than only under static culture. Wound scaffolds could be studied under stretch environments that better reflect mobile anatomical locations. Material degradation could be assessed together with changing tissue mechanics, allowing researchers to determine whether the scaffold transfers load progressively to newly formed tissue. Regenerative rehabilitation adds the patient-level dimension. Instead of treating rehabilitation as a generic protocol introduced once tissue is "healed," rehabilitation intensity might ultimately be matched to scaffold and tissue maturation. During early integration, protection could dominate. As tissue competence improves, controlled loading might become progressively regenerative. Later, higher functional loads may facilitate remodeling toward normal tissue demands. This remains a research hypothesis for oil-palm-derived scaffolds, not an established clinical protocol. Nevertheless, it provides a stronger translational endpoint than simply proposing more in vitro cytocompatibility studies.

Answering RQ4: The Main Translational Bottleneck Is Not Any Single Material Property

The evidence suggests that no single barrier explains why promising nanocellulose materials remain distant from clinical regenerative medicine. Instead, a readiness gap emerges across multiple dimensions, including material standardization, biological validation, preclinical relevance, manufacturing, regulation, and functional assessment. These dimensions interact, so resolving one bottleneck cannot compensate for inadequate evidence elsewhere in the translational chain [19]. The first is material readiness. Researchers need consistent cellulose purity, degree of polymerization, nanoscale dimensions, crystallinity, surface chemistry, and residual-contaminant specifications. Plant biomass is inherently variable, and this variability must be reduced or controlled. The second is biological readiness. Simple cell-viability assays should give way to tissue-specific functional assays. For wound systems, these include epithelial, endothelial, fibroblast, immune, and infection-related models. For bone, they include osteogenic differentiation, vascularization, mineralization, macrophage interactions, and mechanically relevant tissue formation.

The third is preclinical readiness. Animal models should reproduce clinically meaningful defect size, infection status, comorbidity, mechanical environment, and duration. Small-animal success may not predict human loading or remodeling. The fourth is manufacturing readiness. Sterilization, storage, shelf stability, batch reproducibility, process scale-up, quality-control criteria, and economically viable biomedical-grade production must be established. Agricultural feedstock does not remove the need for highly controlled manufacturing. The fifth is regulatory readiness. Product classification, composition, intended use, combination with cells or biologically active substances, sterilization validation, degradation products, and long-term safety can determine the regulatory pathway. The sixth is functional readiness. A regenerative material should eventually demonstrate that the resulting tissue contributes to meaningful function rather than merely producing favorable histology.

Proposed Biomass-to-Function Translational Readiness Framework

The literature therefore supports a seven-stage conceptual framework that treats translation as a cumulative readiness process rather than a simple progression from laboratory fabrication to clinical use. The first stage, biomass readiness, requires reliable OPEFB sourcing, characterization, traceability, and sustainable preprocessing, while the second stage, biomaterial readiness, requires reproducible cellulose or nanocellulose production with controlled chemistry, morphology, purity, and contaminants. The third stage, scaffold readiness, requires application-specific architecture, porosity, mechanical behavior, swelling, degrada-

tion, and sterilizability. The fourth stage, biological readiness, requires evidence that cells not only survive but also perform tissue-appropriate functions, including matrix formation and immune-compatible bioactivity. The fifth stage, regenerative readiness, moves beyond in vitro performance to in vivo evidence of tissue formation, integration, vascularization, remodeling, and an appropriate relationship between tissue formation and scaffold degradation. The sixth stage, functional readiness, requires evidence that regenerated tissue restores relevant mechanical or physiological performance rather than merely producing favorable histological findings. The seventh stage, clinical and regenerative-rehabilitation readiness, adds scalable manufacturing, safety, regulatory compliance, appropriate implantation or use pathways, clinical effectiveness, and evidence-based integration with rehabilitation. Together, the seven stages define progressively more demanding evidence thresholds and make clear why success at an early material stage cannot be treated as proof of clinical readiness.

Figure 5 illustrates the central conceptual contribution of the review. It integrates the circular-bioeconomy origin of the material with the biological and functional standards required for regenerative medicine.

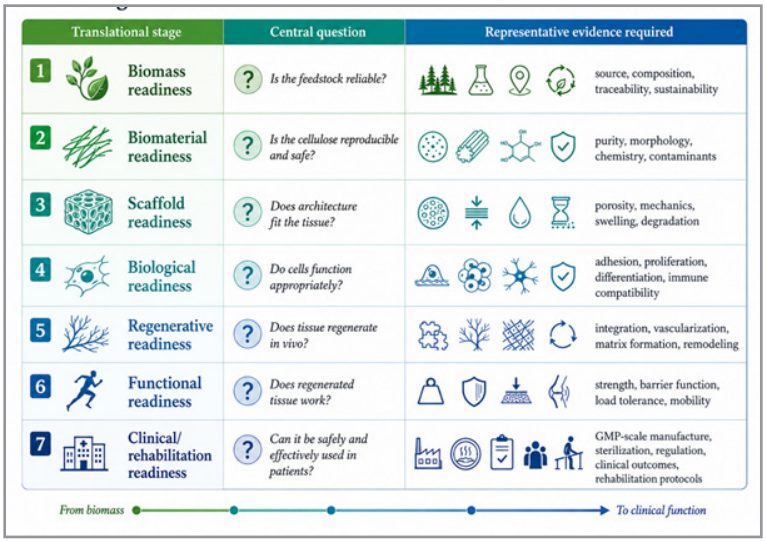

Figure 5: Biomass-to-Function Translational Readiness Framework

The framework prevents a frequent category error in emerging biomaterial research: treating evidence at one readiness stage as proof of later-stage readiness. Excellent nanocellulose yield does not prove scaffold performance; high cell viability does not prove regeneration; regeneration does not prove functional recovery; and functional improvement in animal models does not guarantee scalable human therapy.

Sustainability and Regenerative Medicine Should Be Evaluated Together, Not Separately

An additional insight concerns sustainability. Oil-palm-derived nanocellulose is attractive partly because it valorizes residue that would otherwise have limited value, and contemporary reviews of agro-industrial-waste-derived nanocellulose confirm the broader opportunity to convert heterogeneous residual biomass into higher-value nanomaterials [6-43]. Yet a biomedical product should not be labelled sustainable solely because its feedstock is renewable. Chemical-intensive pretreatment, high energy consumption, solvent use, extensive water purification, freeze-drying, sterilization, and cold-chain storage can materially alter environmental performance. Future research should therefore combine biomedical functionality with life-cycle thinking. Green extraction methods should be compared not only for cellulose yield but also for purity, energy intensity, effluent generation, biological safety, and scalability. Prospective life-cycle assessment shows that some routes described as environmentally benign can perform worse when lower conversion rates or greater reaction-energy requirements offset the advantages of milder solvents; heat integration and by-product recovery can substantially change that balance [53]. A slightly lower-yield method might therefore be preferable if it reduces hazardous reagent use and downstream purification, but that judgment should be supported by system-level environmental evidence rather than by the renewable origin of the feedstock alone. At the same time, medical benefit complicates simple environmental comparisons. A high-value scaffold produced from agricultural waste may justify more intensive processing if it provides meaningful clinical benefit and remains competitive with conventional alternatives. Thus, sustainability assessment should consider environmental burden per unit of medically useful function, not simply per kilogram of material produced.

A Research Agenda for Oil-Palm-Derived Regenerative Scaffolds

The first priority is source-specific validation. Future studies should compare OPEFB-derived CNF, CNC, or CMC directly with better-established cellulose sources under identical scaffold formulations and biological conditions [54-56]. Such comparisons would reveal whether oil-palm origin produces advantages, disadvantages, or functionally negligible differences. Second, research should move beyond generic cytocompatibility. For wound applications, models should include primary human fibroblasts, keratinocytes, endothelial cells, macrophages, bacterial challenge, and ideally chronic-wound conditions. For bone, studies should incorporate mesenchymal stromal cells, osteogenic differentiation, osteoclast-related remodeling, mineralization, vascular interaction, and mechanically relevant loading. Third, scaffold engineering should increasingly incorporate dynamic testing. The development of mechanobiology-informed systems by Entezari et al. [40], Sheehy et al. (2021), and Jiao et al. (2024)

[44] suggests that static testing captures only part of regenerative performance. Future oil-palm cellulose scaffolds intended for musculoskeletal applications should therefore be assessed under controlled strain, compression, or fluid-flow conditions.

Fourth, researchers should connect degradation to tissue formation. Scaffold persistence that is too short may result in structural failure; persistence that is too long may obstruct remodeling. Cao and Ding (2022) [3] emphasize the need to harmonize biomaterial degradation and tissue regeneration.

This principle should become a central design criterion rather than a late-stage measurement. Fifth, biosafety should be evaluated from the beginning. Li et al. (2024) [9] show why impurities and nanoscale effects require systematic attention. Residual bleaching agents, acids, crosslinkers, extractives, endotoxin-like contaminants, metals, and other production-derived compounds should be quantified rather than assumed absent. Finally, regenerative rehabilitation deserves experimental testing. No current evidence justifies claiming that OPEFB scaffolds already improve rehabilitation outcomes. Nevertheless, the mechanobiological literature makes this an appropriate frontier. Future animal studies could compare identical scaffolds under different progressive-loading schedules to determine whether rehabilitation changes integration, vascularization, mineralization, fibrosis, or mechanical strength. Such experiments would provide genuinely new evidence rather than simply repeating material-characterization studies.

Conclusion

Oil palm biomass has the potential to move far beyond its traditional classification as an agricultural residue. OPEFB can serve as a renewable cellulose source, and contemporary research demonstrates that its cellulose can be processed into nanoscale and derivative forms capable of supporting increasingly sophisticated biomaterial architectures. Direct studies already show that OPEFB-derived CNF can be fabricated into highly porous antibacterial bioaerogels compatible with fibroblast proliferation, while OPEFB-derived CMC can contribute to porous scaffolds supporting osteoblast attachment and proliferation.

These findings justify serious consideration of oil-palm-derived cellulose as a regenerative-biomaterial feedstock, but they do not yet justify claims of established clinical tissue regeneration. Most evidence remains at material, in vitro, or early preclinical stages [57]. The larger nanocellulose field shows what may be achievable through biomineralization, hybridization, three-dimensional printing, anisotropy, antimicrobial modification, and mechanically instructive scaffold design, yet such results must be validated directly for OPEFB-derived systems.

The central insight of this review is that the relevant endpoint should not be nanocellulose production or even tissue formation alone. A regenerative scaffold must progress through a continuum from controlled biomass sourcing to biomaterial purity, scaffold architecture, cell–material interaction, tissue-specific regeneration, mechanical integration, functional recovery, and ultimately safe clinical translation. Skin and wound applications appear particularly plausible near-term targets because the hydration, porosity, and modifiability of nanocellulose align naturally with wound-management requirements. Bone tissue engineering represents a more demanding but potentially transformative application in which mineralization, mechanical performance, vascularization, and load adaptation must be solved simultaneously. Regenerative rehabilitation provides an important future horizon. Mechanical loading is not merely something applied after biological healing; it can participate in the biology of repair [58-60]. This suggests a future in which scaffold properties and rehabilitation protocols are designed together, with loading intensity and timing matched to material degradation, tissue integration, and changing mechanical competence.

Future research should therefore prioritize direct comparative evaluation of OPEFB-derived nanocellulose, tissue-specific cell models, immune and vascular responses, in vivo defect studies, dynamic mechanobiological testing, long-term degradation and biosafety, sterilization, reproducible biomedical-grade manufacturing, and regulatory planning. The most consequential advance would be to demonstrate not only that oil-palm-derived cellulose supports cells, but that it helps regenerate tissue capable of restoring meaningful function. Achieving that transition would connect circular biomass valorization with regenerative medicine in its fullest sense: converting agricultural residues into materials that participate in rebuilding living tissue and supporting human recovery.

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