Universal Library of Medical and Health Sciences Research Article

ISSN: 3064-6545 | Volume 4, Issue 3

Open Access | PP: 70-76

DOI: https://doi.org/10.70315/uloap.ulmhs.2026.0403005

Multifunctional Nanoparticle Systems Combining Osteogenic, Angiogenic, and Immunomodulatory Cues in 3D-Printed Bone Scaffolds

Betelhem Solomon Abay

PhD Candidate at New Jersey Institute of Technology, New Jersey, USA.

Abstract

Critical size bone defects remain clinically challenging to treat with current gold standard options, autografting and allografting. 3D printing produces scaffolds that aid the bone's natural regenerative ability by promoting osteogenesis. These scaffolds can be manufactured to spatially control mineral delivery, promote vascular ingrowth, and support immune resolution while retaining a stable printed architecture for as long as scaffold support is needed. 3D-printed scaffolds can be made using different composite ink formulations, including nanoparticles incorporated into printable matrices. This review examines nanoparticle-incorporating 3D-printed bone scaffolds, focusing on nanoscale hydroxyapatite, bioactive glass nanoparticles, ion-releasing inorganic formulations, and polymeric carriers for BMP-2 and VEGF. The article shows the current state of the art on how nanoparticles incorporated into 3D-printed scaffolds are being used to promote osteogenesis, angiogenesis, and delivery of immunomodulatory cues, followed by remaining challenges. A targeted narrative review of ten peer-reviewed publications from 2021 to 2026 supported comparative source analysis, typologization, and conceptual synthesis. The reviewed literature indicates that stronger scaffold concepts connect nanoparticle dispersion, print fidelity, release kinetics, macrophage behavior, vascular support, and mineral maturation. Practical application requires a staged design logic that links material selection with immune monitoring, angiogenic validation, osteogenic assessment, degradation control, and mechanical testing under wet-state conditions.

Keywords: *3D-Printed Scaffolds, Bone Regeneration, Multifunctional Nanoparticles, Osteogenesis, Angiogenesis, Immunomodulation, Bioactive Glass, Nano-Hydroxyapatite, Growth Factor Delivery, Osteoimmunology.*

INTRODUCTION

Critical-size bone defects remain a major orthopedic challenge because spontaneous healing is insufficient and current gold standard treatments, including autografts and allografts, are limited by donor-site morbidity, limited tissue availability, risk of infection, and incomplete functional recovery (Sun et al., 2025; Gharibshahian et al., 2023). Bone regeneration depends on the coordinated progression of several biological processes that occur at different rates. A scaffold can support mineralized matrix formation and still fail if vascular ingrowth remains weak or if the first inflammatory phase does not shift toward tissue repair. Additive manufacturing has changed scaffold design through control over pore geometry, patient-specific shape, strand orientation, and load-bearing architecture. Printed architecture gives the construct form, but form alone does not reproduce the biochemical density of native bone remodeling.

Nanoparticle-functionalized scaffolds address this gap by adding nanoscale biological activity to a printed matrix. Nanoscale hydroxyapatite, bioactive glass nanoparticles, ion-releasing inorganic systems, and polymeric growth-factor carriers can contribute osteoconductive, angiogenic, antimicrobial, antioxidant, or immune-regulating properties. The integration problem remains. A scaffold enriched with one bioactive additive may improve one repair phase while leaving the wider sequence underdeveloped. Bone regeneration is the combined work of inflammatory response at the defect site, proper reconstruction of the vascular system, and the coordinated work of bone cells to organize the signaling cascade needed for healing (Lei et al., 2024; Long et al., 2023; El-Habashy et al., 2021).

This review evaluates multifunctional nanoparticle systems used in 3D-printed bone scaffolds through the combined lens of osteogenic, angiogenic, and immunomodulatory signaling. Three research objectives guide the article. The first objective is to compare major nanoparticle classes by their dominant biological cues and engineering trade-offs. The second objective is to assess how dispersion, spatial

Citation: Betelhem Solomon Abay, "Multifunctional Nanoparticle Systems Combining Osteogenic, Angiogenic, and Immunomodulatory Cues in 3D-Printed Bone Scaffolds", Universal Library of Medical and Health Sciences, 2026; 4(3): 70-76. DOI: https://doi.org/10.70315/uloap.ulmhs.2026.0403005.

placement, and release behavior shape the shift from single-function additives to coordinated multifunctional systems. The third objective is to develop an implementation logic for scaffold design, validation, and monitoring in an analytical review format.

The novelty of this article lies in treating multifunctionality as a design criterion instead of a broad descriptive label. A scaffold reaches functional maturity when its material structure, nanoscale bioactivity, release profile, and immune-vascular-bone sequence work within the same repair logic. The working hypothesis states that nanoparticle-enhanced 3D-printed scaffolds offer the strongest regenerative concept when engineers co-design osteogenic, angiogenic, and immunomodulatory cues around temporal repair phases and manufacturing constraints. A high concentration of one cue cannot compensate for poor dispersion, unstable release, inadequate vascular support, or unresolved inflammatory signaling.

MATERIALS AND METHODS

Materials. The literature search covered PubMed, Scopus, Web of Science, ScienceDirect, Frontiers, SpringerLink, Oxford Academic, and publisher-hosted journal pages. Search terms combined "3D printed scaffold," "bone regeneration," "nanoparticle," "nano-hydroxyapatite," "bioactive glass," "magnesium," "strontium," "silicon," "black phosphorus," "BMP-2," "VEGF," "angiogenesis," "osteogenesis," and "immunomodulation." The initial screening produced 46 records. Thirty-six records were excluded because they fell outside the 2021-2026 period, focused on non-bone tissues, lacked 3D-printed scaffold architecture, used no nanoscale or nanoparticle-based functionalization, duplicated general review material, or discussed material chemistry without a bone-regeneration endpoint. The final corpus contained eleven peer-reviewed publications. The selected sources covered recent reviews of 3D-printed bone scaffolds and polycaprolactone (PCL)-based composites (Gharibshahian et al., 2023; Sun et al., 2025), core–shell hydrogel scaffolds reinforced with hybrid hydroxyapatite/polycaprolactone nanoparticles (El-Habashy et al., 2021), nano-hydroxyapatite scaffolds with drug-loaded microspheres (Li et al., 2023), magnesium- and strontium-containing bioactive glass or bioceramic systems (Dai et al., 2024; Huang et al., 2025; Lei et al., 2024), silicon-doped calcium phosphate scaffolds and epigallocatechin gallate/silicon (EGCG/Si) nanohybrid coatings (Lu et al., 2024; Xiao et al., 2026), black phosphorus-based osteoimmune scaffolds (Long et al., 2023), and bilayer gelatin methacryloyl (GelMA) systems delivering bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF) through poly(lactic-co-glycolic acid) (PLGA) nanoparticles (Alarcin et al., 2025).

Methods. The review applies comparative analysis to separate nanoparticle class, scaffold matrix, biological cue, release mode, and manufacturing risk. Source analysis distinguishes experimentally reported functions from broader interpretive claims. Conceptual synthesis connects osteogenesis, angiogenesis, and immunomodulation into one repair sequence. Typologization supports the classification of nanoparticle strategies, while analytical generalization supports the proposed implementation logic for scaffold development and monitoring.

RESULTS

Recent work on 3D-printed bone scaffolds places scaffold design beyond geometric replacement of missing tissue volume. Researchers now examine material composition, hierarchical porosity, mechanical stability, growth-factor delivery, and clinical scalability as related design demands (Sun et al., 2025). This shift matters for scaffold engineering because the construct enters a living defect where stiffness, degradation, cell migration, perfusion, inflammation, and mineral deposition affect one another. Reviews of PCL-based composites reach a similar point from the polymer side. PCL gives printability, shape retention, and relatively stable mechanical support, while limited intrinsic bioactivity explains why researchers add ceramic particles, growth factors, cells, drugs, and composite modifications to improve biological response (Gharibshahian et al., 2023). Taken together, these review-level sources define the working boundary of this article: 3D printing addresses architecture with increasing precision, while nanoparticle systems address the biological incompleteness of printable matrices.

Nano-hydroxyapatite offers the most direct route for introducing mineral-like cues into printed scaffolds. El-Habashy et al. (2021) showed this logic in extrusion-printed core–shell hydrogel scaffolds reinforced with hybrid hydroxyapatite/polycaprolactone nanoparticles for in vivo bone regeneration. A later dual-nozzle 3D-printed nano-hydroxyapatite scaffold loaded with vancomycin sustained-release microspheres developed the same mineral-cue logic toward localized drug delivery and fabrication control (Li et al., 2023). This design has value beyond antimicrobial delivery. It shows how a printing process can place functional materials inside a spatially organized scaffold while the nanoscale phase creates a mineral environment closer to native bone. The limitation remains clear. Nano-hydroxyapatite mainly supports osteoconduction. Without immune-regulating or angiogenic modules, the scaffold contributes to one part of the repair sequence and leaves the remaining phases dependent on host response or extra additives. This marks the first gap in current multifunctional scaffold design: a scaffold can contain nanoparticles and still remain biologically narrow.

Bioactive glass and ion-releasing ceramic systems move closer to multifunctional behavior because their dissolution products can affect several cell populations. Magnesium-doped micro-nano bioactive glass composite scaffolds have been reported to promote osteogenesis, angiogenesis, and

immunomodulation through Mg, Si, and Ca ion release, with macrophage regulation placed inside the regenerative mechanism (Dai et al., 2024). A related design logic appears in SrBG/PCL scaffolds with a polydopamine coating, where researchers modify a printed PCL structure to improve cell adhesion, osteogenic activity, immune response, and angiogenic performance (Huang et al., 2025). Calcium silicate and calcium sulfate-based printed bioceramics containing decalcified bone matrix add another route to the same design family by connecting biomineralization, M2 macrophage polarization, vascular regeneration, and new bone formation (Lei et al., 2024). Across these systems, ions do more than supply inorganic ingredients for mineral deposition. They influence the local environment in which immune cells, endothelial cells, and osteogenic cells interact.

The same evidence makes uncontrolled ion release a design risk. Silicon-doped biphasic calcium phosphate scaffolds showed that doping level changes phase composition, degradation, porosity, ion release, mechanical behavior, and biological response (Lu et al., 2024). The reported optimum around moderate silicon incorporation carries a direct engineering implication. Multifunctionality has a dosage window. Low release may fail to generate a biological effect, while excessive release or phase instability can disturb differentiation and vascularization. Engineered scaffolds therefore cannot be evaluated by the presence of a regenerative ion alone. The release curve, degradation behavior, mechanical retention, and local tissue tolerance decide whether the ion-based strategy supports repair or creates a new failure point.

Black phosphorus and nanohybrid coating strategies broaden the discussion by shifting attention toward surface activity and osteoimmune programming. A 3D-printed PLAG/black phosphorus scaffold was designed to regulate the osteoimmune microenvironment and osteogenesis, with macrophage phenotype and osteogenic differentiation placed within the same regenerative frame (Long et al., 2023). A multifunctional EGCG/Si nanohybrid-coated PLGA scaffold follows a different route to similar integration. In that system, the silicon component supports osteogenesis and endothelial network formation, while EGCG contributes antioxidant and immune-regulatory effects associated with reparative macrophage behavior and bone formation (Xiao et al., 2026). These examples help move the field away from a purely bulk-additive model. Functionalizing the scaffold surface may reduce some dispersion problems that appear when engineers load particles inside a printable ink or melt. It also creates its own testing demands: coating stability, uniform coverage, sterilization resistance, and degradation behavior under physiological conditions.

Polymeric nanoparticles loaded with growth factors provide the most explicit route for timed biochemical delivery. A bilayer GelMA scaffold containing BMP-2-loaded PLGA nanoparticles in one layer and VEGF-loaded PLGA nanoparticles in another layer was developed to support vascularized bone regeneration in a calvarial defect model (Alarcin et al., 2025). This design assigns BMP-2 and VEGF different biological tasks and uses scaffold architecture to separate osteogenic and angiogenic signaling in space. Microfluidic nanoparticle production, narrow particle-size distribution, controlled release behavior, and bilayer printing create a more disciplined delivery system than direct growth-factor mixing. Yet the model exposes a remaining limitation. It coordinates osteogenic and angiogenic cues, while immune regulation has not been built into the construct as an equal design target. The system advances multifunctionality, but it does not close the whole immune-vascular-bone loop.

A comparison of growth-factor carrier systems, ion-releasing bioactive glass, silicon-based coatings, and silicon-doped ceramics clarifies why controlled release cannot mean slower delivery alone. The BMP-2/VEGF PLGA strategy offers molecular specificity and spatial separation (Alarcin et al., 2025). Magnesium-doped bioactive glass distributes broader ionic signals across immune, vascular, and osteogenic events (Dai et al., 2024). EGCG/Si nanohybrid coatings combine redox control, immune modulation, endothelial response, and mineralizing support at the scaffold interface (Xiao et al., 2026). Silicon-doped calcium phosphate scaffolds show that broad ion-release logic can become unstable when the concentration exceeds the favorable window (Lu et al., 2024). The design conclusion is precise: multifunctionality depends on calibrated release of compatible cues within a defect environment that changes over time.

Manufacturing creates a second axis of comparison. Reviews of PCL composites describe the persistent dependence of printed scaffold performance on matrix selection, blending, and process compatibility (Gharibshahian et al., 2023). Dual-nozzle nano-hydroxyapatite printing demonstrates that spatial fabrication can support combined functions when material streams remain printable and coherent (Li et al., 2023). SrBG/PCL scaffolds with a polydopamine coating show how surface modification can compensate for weak bioactivity and limited cell adhesion in the base polymer (Huang et al., 2025). Composite bioceramic scaffolds show that immunomodulation, vascular response, and mineralization can be built into ceramic-dominant systems, although brittleness, degradation rate, and defect-shape matching remain engineering constraints (Lei et al., 2024). These positions lead to one practical lesson. Nanoparticle selection has to move together with print fidelity, particle distribution, strand integrity, pore interconnectivity, and post-print stability.

Figure 1 presents the cue architecture that emerges from the reviewed literature. It organizes nanoparticle-functionalized scaffolds around three linked biological streams and four engineering checkpoints. The figure is adapted from recent work on 3D-printed scaffold technologies, magnesium-doped bioactive glass scaffolds, and EGCG/Si nanohybrid coatings,

where regenerative performance depends on architecture, nanoscale bioactivity, immune response, vascularization, and mineralization (Dai et al., 2024; Sun et al., 2025; Xiao et al., 2026).

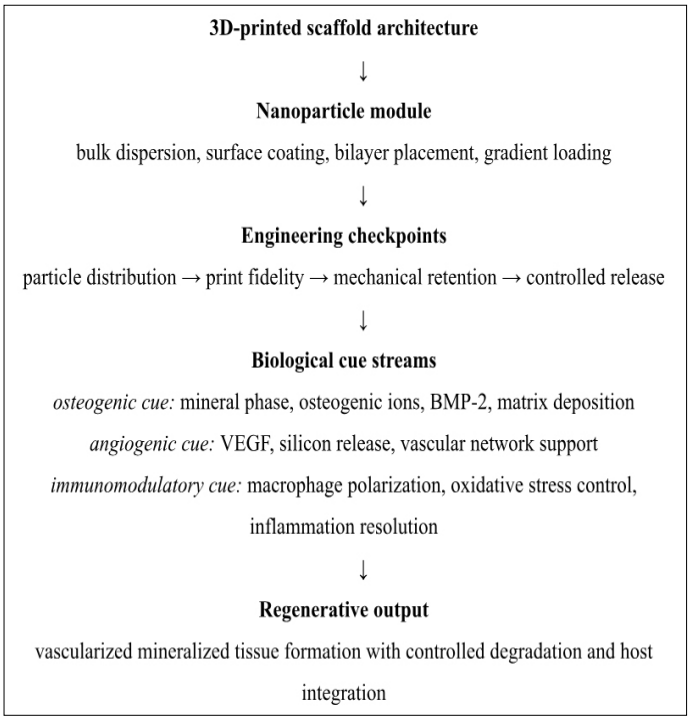

Figure 1. Cue integration pathway for multifunctional nanoparticle-functionalized 3D-printed bone scaffolds (adapted from Dai et al., 2024; Sun et al., 2025; Xiao et al., 2026)

The figure exposes a recurring weakness in the field. Many studies document one or two links in the pathway with convincing evidence, while fewer systems validate the full route from particle placement to immune response, vascular support, mineral maturation, degradation, and mechanical retention. Nano-hydroxyapatite scaffolds handle mineral mimicry well, especially when printing gives controlled architecture (Li et al., 2023). Ion-releasing glass and ceramic systems add immune and vascular influence, but their effects depend on release windows and phase stability (Dai et al., 2024; Lu et al., 2024). Growth-factor nanoparticle systems improve molecular targeting and temporal delivery, but they may treat immune response as a secondary outcome unless the scaffold design assigns macrophage behavior a defined function from the start (Alarcin et al., 2025). Surface coatings and nanohybrids offer a practical route for combining interface-level immune regulation with osteogenic and angiogenic cues (Huang et al., 2025; Xiao et al., 2026). The most convincing systems translate nanoscale function into a scaffold-scale repair sequence.

The reviewed literature supports a typology of four design families. The first family contains mineral-mimetic scaffolds dominated by nano-hydroxyapatite and calcium phosphate cues. These systems support osteoconduction and matrix mineralization, but they usually need additional modules for immune and vascular control. The second family contains ion-releasing bioactive glasses and doped ceramics. Their strength lies in broad biological reach, especially when magnesium, silicon, strontium, calcium, or related ions influence macrophage behavior, endothelial activity, and osteogenic differentiation. Their risk lies in uncontrolled dissolution or mechanically unfavorable phase change. The third family contains polymeric carriers for defined growth factors. These carriers provide molecular precision and localized delivery, yet they can increase regulatory complexity and cost. The fourth family contains surface nanohybrids and responsive coatings. These systems attract interest because they modify the host-material interface without heavily disturbing the printed scaffold core, although coating durability remains a testable variable.

The central result is that multifunctional nanoparticle systems are defined by alignment among scaffold architecture, nanoscale cue release, immune response, vascular formation, and mineral maturation. A printed matrix with uneven particle dispersion cannot deliver reliable biological gradients. A biologically active nanoparticle that weakens mechanical continuity may fail before tissue repair stabilizes. A growth-factor carrier that releases its load too fast may create a short signal pulse instead of a regenerative sequence. A ceramic dopant with excessive ion release may suppress the same cells it was intended to support. These limitations explain why current systems can perform well in isolated assays while still remaining difficult to translate into predictable bone repair.

DISCUSSION

The reviewed field supports a move from material-centered selection to sequence-centered programming. A scaffold for critical bone repair enters a wound environment, meets immune cells first, then has to support blood-vessel formation, osteoprogenitor recruitment, mineral deposition, and gradual load transfer. Nanoparticles improve scaffold performance when engineers place them within this biological order. Without such ordering, multifunctionality becomes a label attached to a mixture of materials.

Previous studies have advanced the field by showing that different nanoparticle systems can improve specific regenerative functions. Mineral nanoparticles support matrix-related behavior. Ion-releasing systems can influence inflammation, vascularization, and bone formation through dissolution products. Growth-factor carriers create more precise signaling than direct loading. Coatings and nanohybrids alter the interface where cells first contact the scaffold. The unresolved task lies between demonstrating several useful effects and building a scaffold that coordinates those effects under manufacturing and clinical constraints. The next research stage needs to treat immune response, vascular growth, and osteogenesis as a staged process with measurable gates.

A practical implementation model begins with the defect profile. The first decision concerns load environment, defect size, expected degradation period, and vascular risk. The second decision concerns the printable matrix. PCL-dominant systems suit designs that require structural persistence and reliable printing. Ceramic-rich systems suit designs where osteoconductive behavior and ion release carry more weight. The third decision concerns nanoparticle placement. Bulk dispersion fits designs that need uniform biological activity, but it increases the demand for rheological control and dispersion testing. Surface coating fits designs aimed at the early host-material interface. Bilayer or gradient placement fits designs where angiogenic and osteogenic cues require spatial separation.

Release design forms the fourth decision. Growth-factor systems require attention to burst release, retention of bioactivity, dose economy, and spatial confinement. Ion-releasing systems require attention to dissolution rate, pH shift, phase stability, and dose tolerance. Coating-based systems require attention to adhesion, sterilization resistance, and degradation under physiological flow. The fifth decision concerns validation. No single biological assay can support a multifunctional claim. A scaffold that claims osteogenic, angiogenic, and immunomodulatory action needs a matched panel of immune, vascular, mineralization, mechanical, and degradation metrics. The purpose of Table 1 is to compare nanoparticle strategies by design value, cue profile, engineering risk, and likely scaffold placement. The comparison does not rank materials as universally superior. It indicates which scaffold problem each strategy addresses most directly and where design failure is most likely to occur.

Table 1. Functional comparison of nanoparticle strategies for 3D-printed bone scaffolds (compiled by the author based on Alarcin et al., 2025, Dai et al., 2024, Gharibshahian et al., 2023, Huang et al., 2025, Lei et al., 2024, Li et al., 2023, Long et al., 2023, Lu et al., 2024, Sun et al., 2025, and Xiao et al., 2026)

Nanoparticle strategy	Dominant design value	Cue profile	Main engineering risk	Preferred scaffold placement
Nano-hydroxyapatite and calcium phosphate nanoparticles	Mineral mimicry and osteoconduction	Strong osteogenic support, weaker direct immune and vascular control	Agglomeration, brittle behavior at high loading, uneven mineral distribution	Bulk dispersion in printable polymer or ceramic composite
Bioactive glass and doped bioceramic nanoparticles	Ion-mediated coupling of bone, vessel, and immune response	Osteogenic, angiogenic, and immunomodulatory potential through controlled dissolution	Excessive ion release, phase instability, degradation mismatch	Bulk dispersion, ceramic composite phase, local concentration gradients
Metal, semiconductor, and oxide-like ion-releasing nanosystems	Interface activity, redox modulation, immune response control	Immune regulation combined with osteogenic or vascular stimulation	Long-term particle fate, dose sensitivity, coating or matrix instability	Surface coating, embedded nanoscale phase, responsive layer
Polymeric nanoparticles carrying BMP-2 or VEGF	Timed molecular delivery and spatial cue separation	Strong osteogenic or angiogenic specificity, immune cue depends on added design	Burst release, protein degradation, regulatory complexity	Bilayer printing, microgel inclusion, compartmentalized placement
Nanohybrid surface coatings	Early host-material interface programming	Combined osteogenic, angiogenic, antioxidant, and immune-regulatory action	Coating durability, sterilization effects, uneven surface coverage	Post-print coating, layer-by-layer assembly, functionalized pore walls

The table suggests that scaffold development needs to start from the missing biological function, not from the most current nanoparticle trend. If the defect is expected to suffer from poor vascular ingrowth, a scaffold with mineral nanoparticles alone will probably remain insufficient. If excessive inflammation is expected, the design needs an immune-facing module from the start. If the mechanical envelope is narrow, the nanoparticle system needs selection only after print fidelity and compressive behavior have been tested. The most promising design is often hybrid, but hybridization needs control. Adding more components can blur release kinetics and make failure mechanisms harder to identify. The purpose of Table 2 is to translate the review into a development and monitoring sequence. The table compares development gates, evidence requirements, practical metrics, and decision rules for scaffold evaluation. It can guide analytical review work and future experimental protocol design.

Table 2. Development and monitoring logic for multifunctional nanoparticle-functionalized 3D-printed bone scaffolds (compiled by the author based on Alarcin et al., 2025, Dai et al., 2024, Gharibshahian et al., 2023, Huang et al., 2025, Lei et al., 2024, Li et al., 2023, Long et al., 2023, Lu et al., 2024, Sun et al., 2025, and Xiao et al., 2026)

Development gate	Required evidence	Practical metric	Decision rule
Printability	Stable extrusion or printing without collapse	Strand width, pore regularity, shape fidelity, rheological stability	Continue only if architecture remains reproducible after nanoparticle addition
Nanoparticle distribution	Uniform or intentionally patterned placement	Microscopy, elemental mapping, particle-size distribution, agglomerate assessment	Redesign mixing or coating if local clusters distort mechanics or release
Release behavior	Sustained and biologically tolerable cue delivery	Ion release curve, protein release curve, burst fraction, degradation profile	Advance only when release duration matches the target repair phase
Immune response	Shift from damaging inflammation toward repair-associated phenotype	Macrophage phenotype, cytokine balance, oxidative stress indicators	Treat immune failure as a design failure, not as a secondary observation
Angiogenic response	Evidence of endothelial support and network formation	Endothelial migration, tube formation, CD31-related staining, perfusion proxies	Require vascular evidence before claiming large-defect relevance
Osteogenic response	Matrix maturation and mineral deposition	ALP activity, RUNX2, osteocalcin, mineral staining, micro-CT bone parameters	Interpret mineralization together with vascular and immune results
Mechanical retention	Structural adequacy during degradation	Compressive modulus, strength retention, fatigue behavior, wet-state stability	Reject formulations that trade biological activity for early mechanical failure
Safety and translational readiness	Low toxicity and predictable degradation products	Cell viability, local pH, ion excess, residual solvent, sterilization stability	Advance only when biological benefit is not coupled with avoidable toxicity

This decision logic changes the measurement of multifunctionality. A scaffold should not receive a multifunctional designation because separate assays show isolated positive effects. The designation is justified when the immune, vascular, osteogenic, mechanical, and release data align. A material that stimulates osteogenic markers while delaying endothelial network formation remains incomplete for critical defect repair. A scaffold that shifts macrophage behavior but loses pore architecture during degradation faces the same limitation. Validation has to be cumulative and conditional.

Several limitations shape the interpretation of this review. The five-year source window improves recency but narrows historical coverage of foundational scaffold chemistry. The selected studies differ in scaffold matrix, printing technique, defect model, cell type, animal model, and endpoint duration. These differences prevent direct quantitative comparison. Most reviewed systems remain preclinical, and their performance in human defects cannot be inferred without caution. Another limitation concerns the use of the term "multifunctionality." Researchers apply the term with different levels of strictness. Some use it for combined material and biological properties, while others demonstrate coordinated immune, vascular, and osteogenic behavior. This article applies the stricter interpretation.

Previous studies provide enough evidence to support the direction of the field, but they do not settle the best scaffold formula. The evidence favors a design philosophy. Mineral mimicry, ion release, growth-factor delivery, surface chemistry, and printed architecture need assembly according to the repair phase each component is meant to control. A mature scaffold platform would contain a mechanically reliable printed backbone, a reproducible nanoparticle distribution strategy, an early immunomodulatory signal, an angiogenic support module, and a longer osteogenic cue. Such a system would be easier to evaluate because each functional claim would be tied to a measurable gate.

CONCLUSION

Multifunctional nanoparticle systems for 3D-printed bone scaffolds differ in the regenerative functions they support. Nano-hydroxyapatite and calcium phosphate particles remain strong tools for mineral mimicry and osteoconduction. Bioactive glass, doped ceramics, and ion-releasing inorganic systems provide broader biological reach because their dissolution products can influence immune, vascular, and

osteogenic behavior. Polymeric nanoparticles carrying BMP-2 or VEGF give greater control over molecular delivery, especially when the printed construct separates cues in space. Nanohybrid coatings and surface-functionalized systems offer a promising route for early host-material interface programming.

The transition from single-function scaffolds to coordinated multifunctional systems depends on dispersion, spatial placement, release kinetics, and mechanical retention. The reviewed studies support the view that the same nanoparticle can produce different outcomes when concentration, phase stability, degradation rate, and scaffold architecture change. Multifunctionality therefore requires controlled relationships among material behavior, biological timing, and manufacturing reproducibility.

The hypothesis proposed in the introduction is supported. Nanoparticle-enhanced 3D-printed scaffolds become more convincing when osteogenic, angiogenic, and immunomodulatory cues are co-designed around the temporal sequence of repair and verified through matched monitoring metrics. The strongest future direction lies in disciplined engineering of cue timing, scaffold architecture, interface response, and validation gates within one reproducible platform.

REFERENCES

1. Alarcin, E., Akguner, Z. P., Ozturk, A. B., Yasayan, G., Ilhan-Ayisigi, E., Kazan, A., Yesil-Celiktas, O., Akcora, D. S., Akakin, D., Kocaaga, B., Eren, G., Gunes, K., Kerimoglu, O., Seki, H. K., & Guner, F. S. (2025). Biomimetic 3D bioprinted bilayer GelMA scaffolds for the delivery of BMP-2 and VEGF exogenous growth factors to promote vascularized bone regeneration in a calvarial defect model in vivo. *International Journal of Biological Macromolecules, 306*, 141440. https://doi.org/10.1016/j.ijbiomac.2025.141440
2. Dai, K., Zhao, F., Zhang, W., Chen, D., Hang, F., Zou, X., & Chen, X. (2024). 3D-printed magnesium-doped micro-nano bioactive glass composite scaffolds repair critical bone defects by promoting osteogenesis, angiogenesis, and immunomodulation. *Biomedical Materials, 19*(6), 065028. https://doi.org/10.1088/1748-605X/ad7e8e
3. El-Habashy, S. E., El-Kamel, A. H., Essawy, M. M., Abdelfattah, E.-Z. A., & Eltaher, H. M. (2021). Engineering 3D-printed core–shell hydrogel scaffolds reinforced with hybrid hydroxyapatite/polycaprolactone nanoparticles for in vivo bone regeneration. *Biomaterials Science, 9*(11), 4019–4039. https://doi.org/10.1039/D1BM00062D
4. Gharibshahian, M., Salehi, M., Beheshtizadeh, N., Kamalabadi-Farahani, M., Atashi, A., Nourbakhsh, M.-S., & Alizadeh, M. (2023). Recent advances on 3D-printed PCL-based composite scaffolds for bone tissue engineering. *Frontiers in Bioengineering and Biotechnology, 11*, 1168504. https://doi.org/10.3389/fbioe.2023.1168504
5. Huang, Q., Li, X., Fan, Q., Du, Q., Zhao, G., Lv, Y., Wang, Y., Xu, W., & Wa, Q. (2025). Immunomodulation and bone repair of 3D printed Seb/PCL scaffolds containing PDA coating. *International Journal of Bioprinting*. Advance online publication. https://doi.org/10.36922/IJB025210211
6. Lei, Q., Gao, S., Sun, N., Zhang, T., Xiao, L., Huang, H., Chen, Y., Cai, L., & Yan, F. (2024). Immunomodulation, angiogenesis and osteogenesis based 3D-printed bioceramics for high-performance bone regeneration. *Materials & Design, 238*, 112732. https://doi.org/10.1016/j.matdes.2024.112732
7. Li, J., Li, K., Du, Y., Tang, X., Liu, C., Cao, S., Zhao, B., Huang, H., Zhao, H., Kong, W., Xu, T., Shao, C., Shao, J., Zhang, G., Lan, H., & Xi, Y. (2023). Dual-nozzle 3D printed nano-hydroxyapatite scaffold loaded with vancomycin sustained-release microspheres for enhancing bone regeneration. *International Journal of Nanomedicine, 18*, 307–322. https://doi.org/10.2147/IJN.S394366
8. Long, J., Yao, Z., Zhang, W., Liu, B., Chen, K., Li, L., Teng, B., Du, X., Li, C., Yu, X., Qin, L., & Lai, Y. (2023). Regulation of osteoimmune microenvironment and osteogenesis by 3D-printed PLGA/black phosphorus scaffolds for bone regeneration. *Advanced Science, 10*(28), 2302539. https://doi.org/10.1002/advs.202302539
9. Lu, T., Li, G., Zhang, L., Yuan, X., Wu, T., & Ye, J. (2024). Optimizing silicon doping levels for enhanced osteogenic and angiogenic properties of 3D-printed biphasic calcium phosphate scaffolds: An in vitro screening and in vivo validation study. *Materials Today Bio, 28*, 101203. https://doi.org/10.1016/j.mtbio.2024.101203
10. Sun, J., Chen, C., Zhang, B., Yao, C., & Zhang, Y. (2025). Advances in 3D-printed scaffold technologies for bone defect repair: Materials, biomechanics, and clinical prospects. *BioMedical Engineering OnLine, 24*(1), 51. https://doi.org/10.1186/s12938-025-01381-w
11. Xiao, S., Qi, L., Wei, J., Liu, H., Ding, S., Chen, J., Yang, J., Lin, H., & Lu, D. (2026). A multifunctional EGCG/Si nanohybrid-coated 3D-printed porous scaffold for bone defect repair. *Regenerative Biomaterials, 13*, rbag035. https://doi.org/10.1093/rb/rbag035