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Ultrasound-Activated Biomaterials for Spatiotemporal Drug Delivery and Regenerative Medicine

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Abstract: Ultrasound (US) has evolved from a predominantly diagnostic modality into a versatile therapeutic stimulus capable of controlling biological and material responses with considerable spatial and temporal precision. Ultrasound-activated biomaterials integrate acoustic energy with responsive carriers, hydrogels, nanoparticles, microbubbles, nanodroplets, and electroactive scaffolds to enable externally controlled drug release, gene delivery, barrier modulation, and tissue regeneration. The principal mechanisms include stable and inertial cavitation, acoustic streaming, radiation force, localized heating, sonoporation, mechanotransduction, and sonochemical generation of reactive oxygen species. These mechanisms can be exploited independently or in combination to generate pulsatile, delayed, sustained, or on-demand release profiles. Microbubbles and phase-change nanodroplets are particularly attractive because they efficiently convert acoustic energy into mechanical effects, whereas liposomes, polymeric nanoparticles, micelles, and hydrogels provide versatile platforms for transporting small molecules, nucleic acids, proteins, and cells. In regenerative medicine, low-intensity pulsed ultrasound and ultrasound-responsive scaffolds can modulate osteogenesis, angiogenesis, wound healing, stem-cell differentiation, and neural repair. However, acoustic heterogeneity, material polydispersity, bioeffects, immunogenicity, manufacturing reproducibility, and regulatory classification remain important barriers to clinical translation. This mini-review summarizes the physical mechanisms underlying ultrasound activation, discusses major classes of responsive biomaterials, examines applications in spatiotemporal drug delivery and regenerative medicine, and outlines design, safety, and translational considerations. Future progress will depend on standardized acoustic dosimetry, multimodal imaging, adaptive ultrasound control, scalable manufacturing, and biomaterials capable of integrating therapeutic delivery with tissue-specific biological signaling.

Keywords: Ultrasound-Responsive Biomaterials; Spatiotemporal Drug Delivery; Microbubbles; Nanodroplets; Hydrogels; Sonoporation

1. Introduction

The ability to administer therapeutic agents at the correct location and time is a central objective of modern drug-delivery research. Conventional systemic administration frequently exposes healthy tissues to pharmacologically active compounds while only a fraction of the administered dose reaches the intended target. Stimuli-responsive delivery systems address this limitation by coupling therapeutic release to an external or endogenous trigger. Among externally applied stimuli, ultrasound is particularly attractive because it can penetrate soft tissue, can be focused, is widely available clinically, and can be delivered repeatedly without ionizing radiation [1,2].

Ultrasound-activated biomaterials extend this concept by combining acoustic energy with engineered materials whose physical, chemical, or mechanical properties change following insonation. The resulting systems can generate localized release of drugs, proteins, nucleic acids, or other therapeutic signals while limiting exposure elsewhere [3–5]. The uploaded literature synthesis identifies cavitation, acoustic streaming, radiation force, heating, sonoporation, and mechanotransduction as the principal mechanisms through which ultrasound interacts with biomaterials and biological tissues.

The spatial selectivity of ultrasound is determined by the acoustic field and transducer geometry, whereas temporal control is established by the duration, pulse sequence, intensity, frequency, and repetition of insonation. Thus, ultrasound can potentially function as a non-invasive "remote switch" for biomaterials. Depending on the carrier architecture, a single pulse may produce a rapid burst, whereas repeated low-energy exposures can generate multiple release events [6–11].

The field encompasses several material classes, including lipid- or polymer-shelled microbubbles, phase-change nanodroplets, liposomes, polymeric nanoparticles, micelles, hydrogels, nanocomposites, piezoelectric scaffolds, and sonosensitizers [12–18]. Their applications range from cancer therapy and central nervous system (CNS) drug delivery to wound healing, bone regeneration, cartilage repair, cardiovascular therapy, and neural tissue engineering [19–24].

Importantly, ultrasound should not be considered simply as a mechanical trigger. Acoustic exposure can directly influence cells through mechanotransduction and can modify the extracellular environment through fluid flow, radiation force, and cavitation. Consequently, responsive biomaterials can be designed to deliver therapeutic payloads while simultaneously exploiting ultrasound-induced biological signaling [25–30]. This convergence of drug delivery, materials science, and mechanobiology creates opportunities for integrated therapeutic platforms.

2. Physical Basis of Ultrasound Activation

Ultrasound consists of mechanical pressure waves that propagate through biological tissues and biomaterials. Their interaction with matter depends on acoustic frequency, pressure amplitude, pulse duration, duty cycle, intensity, tissue properties, and the presence of gas-containing structures. These variables determine whether the dominant biological response is mechanical, thermal, or chemical [31–35].

2.1 Cavitation

Cavitation is one of the most important mechanisms in ultrasound-mediated drug delivery. In stable cavitation, pre-existing gas bodies or microbubbles undergo repeated oscillation without catastrophic collapse. Their oscillatory motion generates localized microstreaming and shear stress, which can increase membrane permeability and disturb nearby carrier structures [4,5]. At higher acoustic pressures, inertial cavitation can occur. Rapid bubble expansion followed by collapse produces shock waves, microjets, local pressure gradients, and transient high-energy regions. These effects can disrupt polymeric shells, destabilize lipid membranes, deform extracellular matrices, and transiently permeabilize cell membranes [4,23,31]. Cavitation is therefore a powerful mechanism for converting relatively remote acoustic energy into localized mechanical activity.

However, cavitation also represents an important safety consideration. Excessive cavitation may result in vascular injury, hemolysis, hemorrhage, or unwanted tissue damage.

The biological outcome depends strongly on acoustic pressure, frequency, pulse duration, bubble concentration, and tissue environment [31–35].

2.2 Acoustic Streaming and Radiation Force

Acoustic streaming is a steady fluid movement generated by momentum transfer from an acoustic field. Near oscillating microbubbles, surfaces, or particles, streaming can produce localized vortices and shear fields that enhance mixing and mass transport [11,31]. This effect may improve drug transport through tissue and increase contact between carriers and target cells. Acoustic radiation force provides another means of manipulating particles, bubbles, cells, and other structures. Spatial gradients in acoustic intensity can displace suspended objects and concentrate carriers near vessel walls or selected tissue regions [11]. Such effects are particularly relevant to microbubble-mediated delivery and ultrasound-assisted transport of nanocarriers.

2.3 Thermal Effects

Ultrasound energy can be converted into heat through acoustic absorption. At sufficiently high intensities, as in high-intensity focused ultrasound (HIFU), thermal energy can produce hyperthermia or tissue ablation [12]. Conversely, controlled mild heating can be exploited to trigger thermosensitive liposomes, polymers, and hydrogels. The distinction between mechanical and thermal ultrasound exposure is therefore central to biomaterial design. Low-intensity pulsed ultrasound generally emphasizes mechanical stimulation, whereas high-intensity exposures can produce substantial temperature elevation. Appropriate control of duty cycle and pulse duration can reduce heat accumulation while maintaining repeated mechanical activation [12,31–35].

2.4 Sonoporation and Mechanotransduction

Sonoporation refers to transient increases in cellular membrane permeability induced by ultrasound, frequently in association with cavitation. Transient membrane pores can increase intracellular delivery of drugs, proteins, DNA, RNA, and other macromolecules [26,27]. At lower intensities, mechanical stimulation can also activate cellular mechanosensing pathways without causing membrane disruption. Integrins, ion channels, cytoskeletal structures, and downstream signaling networks can respond to acoustic forces. These effects provide a mechanobiological basis for ultrasound-assisted tissue regeneration [16,28,29].

2.5 Sonochemical Effects

Inertial cavitation may promote sonolysis and formation of reactive oxygen species (ROS). Sonosensitizers can amplify this response, providing the basis of sonodynamic therapy. Porphyrins, semiconductor particles, metal-containing nanostructures, and related materials have been investigated as ultrasound-activated ROS-generating agents [24,30]. Thus, ultrasound can activate biomaterials through a spectrum of mechanisms rather than a single pathway.

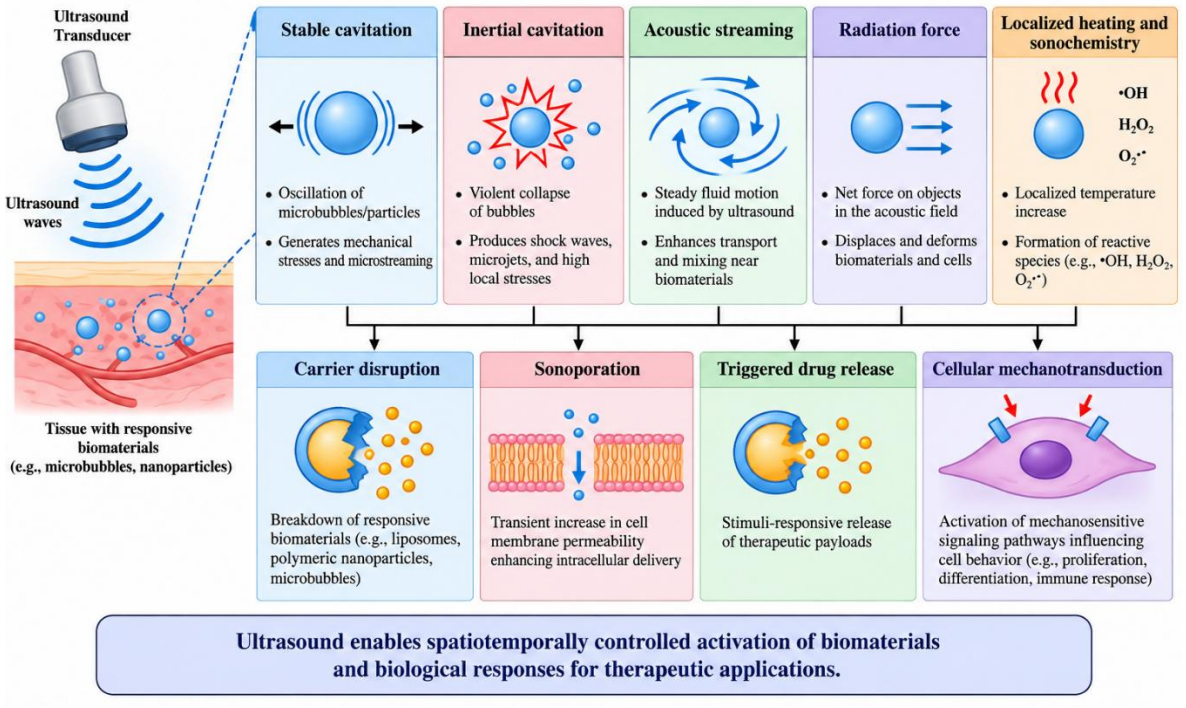

Figure 1. Conceptual mechanisms of ultrasound activation.

Ultrasound propagates through tissue and interacts with responsive biomaterials through stable or inertial cavitation, acoustic streaming, radiation force, localized heating, and sonochemical processes. These effects can disrupt carriers, promote sonoporation, trigger drug release, or activate cellular mechanotransduction.

3. Major Classes of Ultrasound-Activated Biomaterials

The characteristics of major ultrasound-responsive biomaterials are summarized in Table 1.

3.1 Microbubbles

Microbubbles are gas-filled structures, commonly approximately 1–10 μm in diameter, surrounded by lipid, protein, or polymeric shells. Their gas–liquid interface provides strong acoustic responsiveness, making them established ultrasound contrast agents and important therapeutic carriers [7,8]. Upon insonation, microbubbles oscillate or collapse, producing mechanical effects capable of enhancing vascular permeability, disrupting carrier shells, and promoting sonoporation. Therapeutic molecules can be incorporated into the shell, attached to the bubble surface, or co-administered with other nanoparticles [7,36]. Microbubble–nanoparticle complexes can therefore combine the favorable loading characteristics of nanocarriers with the acoustic responsiveness of gas-filled agents. An important advantage is rapid on-demand activation. However, microbubbles generally have relatively short circulation times and can exhibit variations in size, shell composition, and stability. Such heterogeneity may produce variability in acoustic response and therapeutic dose [7,8,36].

3.2 Phase-Change Nanodroplets

Phase-change nanodroplets contain a liquid perfluorocarbon core that can undergo acoustic droplet vaporization (ADV) to form a gas bubble. Unlike preformed microbubbles, nanodroplets can potentially circulate or extravasate in a liquid state before acoustic activation [37–39]. Their vaporization threshold depends on perfluorocarbon composition, droplet size, shell properties, temperature, and acoustic pressure. ADV provides a mechanism for generating bubbles at the target site, thereby combining nanoscale transport with microscale acoustic activity [37–39]. Nevertheless, reproducible control of vaporization, post-vaporization bubble size, persistence, and safety remains necessary before broad clinical translation [38,39].

3.3 Liposomes and Lipid Nanoparticles

Liposomes consist of phospholipid bilayers surrounding aqueous compartments and can encapsulate both hydrophilic and hydrophobic drugs. Ultrasound can destabilize liposomal membranes through mechanical and thermal effects, producing externally controlled drug release [40–43]. Lipid composition is particularly important. Membrane fluidity, lipid phase-transition behavior, PEGylation, and molecular packing can influence ultrasound sensitivity [40,41]. Thermosensitive liposomes can exploit mild acoustic heating, whereas mechanically responsive liposomes can exploit cavitation or acoustic interactions [42,43]. Their relatively high biocompatibility and established pharmaceutical manufacturing experience make liposomes attractive candidates for translation, although robust and reproducible ultrasound-triggered release remains challenging.

3.4 Polymeric Nanoparticles and Micelles

Polymeric nanoparticles and micelles can provide high drug-loading capacity, prolonged circulation, and tunable degradation. Their response to ultrasound may arise from mechanical deformation, local heating, cavitation-assisted disruption, or incorporation of gas-generating components [44–46]. Conventional nanoparticles lack a gas–liquid interface and may therefore require higher acoustic energies than microbubble-containing systems. Hybrid approaches address this limitation by coupling nanoparticles to microbubbles or incorporating acoustically responsive domains [44–46].

3.5 Hydrogels

Hydrogels are particularly attractive for regenerative medicine because they can form three-dimensional matrices that support cells while retaining drugs and proteins. Ultrasound can alter hydrogel structure through mechanical deformation, cavitation, thermal effects, or disruption of reversible crosslinks [14,47,48]. Responsive hydrogels can therefore combine structural support with externally triggered release. For example, ultrasound-sensitive crosslinks can provide burst release of growth factors, while embedded nanoparticles or microcapsules can generate secondary release events [14,47,48].

3.6 Piezoelectric and Electroactive Biomaterials

Piezoelectric materials generate electrical polarization in response to mechanical deformation. When incorporated into scaffolds, ultrasound-induced cyclic deformation can therefore generate local electrical signals without implanted electrodes [10,49]. Materials such as poly(vinylidene fluoride), barium titanate, and related piezoelectric composites have been explored for bone, neural, and soft-tissue regeneration. The generated electrical cues can influence ion channels, cell adhesion, proliferation, differentiation, and angiogenesis [10,49]. Recent work has further demonstrated ultrasound-activated piezoelectric scaffolds capable of simultaneously influencing inflammatory signaling and osteogenesis, illustrating the potential of acoustically controlled electro-mechanical biomaterials [50].

3.7 Sonosensitizers

Sonosensitizers are materials or molecules that generate ROS after ultrasound exposure. Their principal application is sonodynamic therapy, although they may also be incorporated into multifunctional therapeutic platforms [24,30].

Table 1. Comparison of major ultrasound-activated biomaterial classes.

Material class	Main activation mechanism	Typical payload/function	Spatial/temporal control	Major advantages	Key limitations

Microbubbles	Cavitation, radiation force, sonoporation	Drugs, genes, proteins	High; rapid on/off activation	Strong acoustic response; clinically established imaging use	Short circulation; size heterogeneity; cavitation safety
Phase-change nanodroplets	Acoustic droplet vaporization	Drugs, imaging agents	High; activation after vaporization	Nanoscale transport with bubble generation at target	Vaporization control and safety
Liposomes	Mechanical and thermal membrane disruption	Hydrophilic/ hydrophobic drugs	Moderate–high	High biocompatibility; versatile loading	May require relatively high acoustic energy
Polymeric nanoparticles /micelles	Mechanical, thermal, cavitation-assisted release	Small molecules, proteins, nucleic acids	Moderate–high	Tunable degradation and loading	Limited intrinsic acoustic sensitivity
Hydrogels	Mechanical deformation, heating, crosslink disruption	Drugs, proteins, cells	Moderate; can support repeated release	Tissue support and local depot formation	Diffusion limitations and variable acoustic penetration
Piezoelectric scaffolds	Ultrasound-to-electric conversion	Cellular stimulation, regenerative signals	Moderate–high	Wireless electrostimulation	Material safety, fatigue, manufacturing complexity
Sonosensitizers	Cavitation/sonochemical ROS generation	ROS-mediated therapy	High with focused/pulsed US	Non-invasive therapeutic activation	Oxidative toxicity and incomplete mechanistic standardization

Note: *MI, mechanical index; US, ultrasound. Values are qualitative because acoustic thresholds depend strongly on formulation, tissue environment, transducer characteristics, and exposure conditions.*

4. Design Principles for Spatiotemporal Control

The central engineering objective is to establish a predictable relationship among material properties, ultrasound parameters, and therapeutic output. The acoustic activation threshold should be sufficiently low to minimize tissue injury while remaining sufficiently high to prevent unintended release during circulation [3,6,11].

4.1 Material Parameters

Particle size, shell thickness, composition, elasticity, surface charge, phase-transition temperature, viscosity, and gas-core composition can all affect acoustic responsiveness. For microbubbles, shell stiffness and diameter influence resonance and cavitation behavior [7,8]. For nanodroplets, perfluorocarbon chemistry and droplet size influence vaporization thresholds

[37–39]. For liposomes, membrane composition controls susceptibility to mechanical and thermal disruption [40–43].

4.2 Ultrasound Parameters

Frequency, peak negative pressure, intensity, pulse duration, pulse-repetition frequency, and duty cycle determine the delivered acoustic dose. Lower frequencies can promote stronger cavitation, whereas higher frequencies may offer improved spatial resolution. Pulsed exposure can reduce thermal accumulation and permit repeated release cycles [3,11,31].

Focused ultrasound can additionally compensate for the limited spatial selectivity of systemic drug administration by concentrating acoustic energy in a predefined region. The use of phased arrays can further enable beam steering and adaptive focusing.

4.3 Multistage and Multimodal Design

Combining multiple responsive mechanisms may provide greater control than relying on a single trigger. For example, a microbubble can amplify cavitation near a nanoparticle or hydrogel, while a thermosensitive liposome can provide a second release mechanism. Such systems may permit sequential or hierarchical release of different therapeutic agents [6,44].

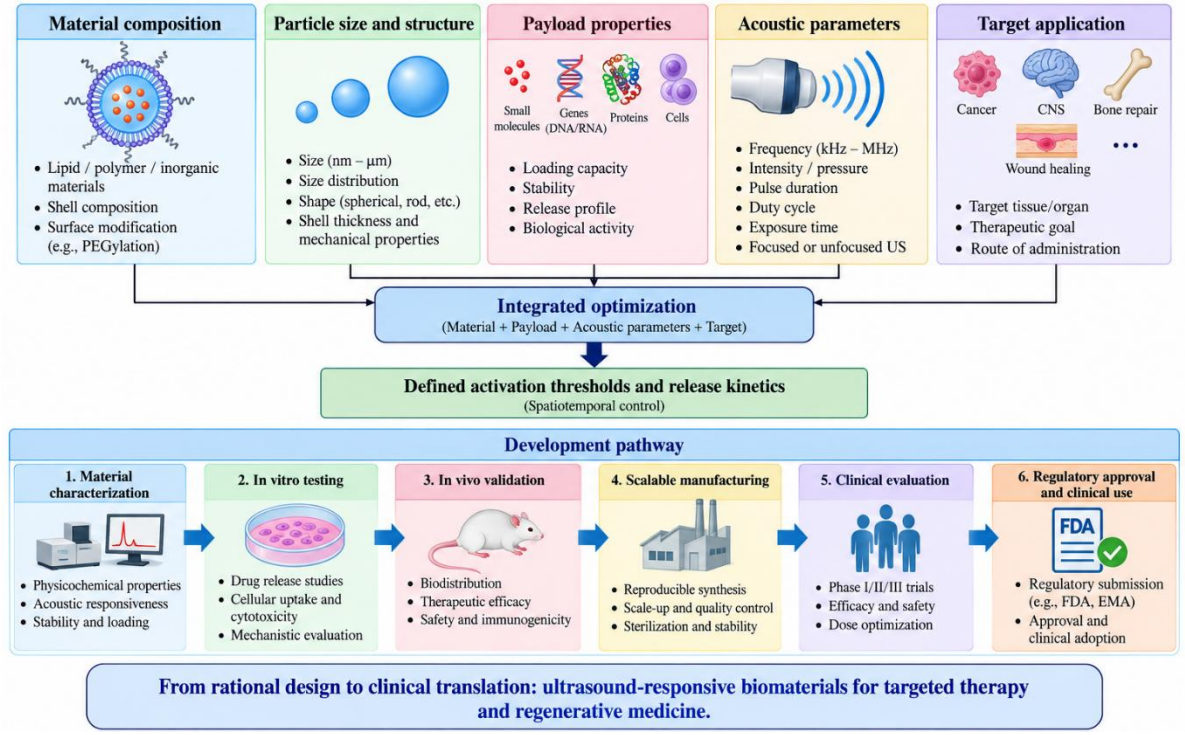

Figure 2. Design roadmap for ultrasound-responsive biomaterials.

Material composition, particle size, shell mechanics, payload properties, and acoustic parameters are jointly optimized to define activation thresholds and release kinetics. The development pathway progresses from material characterization and in vitro testing to animal validation, scalable manufacturing, clinical evaluation, and regulatory approval.

5. Applications in Spatiotemporal Drug Delivery

5.1 Cancer Therapy

Cancer is one of the most extensively investigated applications of ultrasound-mediated delivery. Tumor therapy is limited by abnormal vasculature, dense extracellular matrix, elevated interstitial pressure, and heterogeneous drug distribution. Focused ultrasound combined with microbubbles can enhance vascular permeability and facilitate extravasation of therapeutic agents [36,51]. Microbubble-mediated ultrasound can also improve transport through the tumor interstitium and enhance cellular uptake through sonoporation [51,52]. Liposomes, polymeric nanoparticles, and micelles can be activated within the focused region,

potentially increasing local drug concentrations while reducing systemic exposure [44,45]. Ultrasound-triggered sonodynamic therapy provides an alternative mechanism in which acoustic energy activates sensitizers to generate ROS. This approach can complement chemotherapy, immunotherapy, or HIFU-based tumor treatment [24,30,53].

5.2 Central Nervous System Delivery

The blood–brain barrier (BBB) represents one of the most important obstacles to pharmacological treatment of CNS diseases. Focused ultrasound combined with circulating microbubbles can produce transient and reversible BBB opening through controlled cavitation [54–57]. This approach has been investigated for delivery of antibodies, nanoparticles, chemotherapeutics, genes, and other macromolecules. Recent reviews of clinical investigations emphasize the increasing number of studies examining FUS-mediated BBB opening for brain tumors and neurodegenerative diseases [54–57]. Importantly, BBB opening requires careful control of acoustic pressure and bubble activity. Excessive cavitation can produce vascular damage, whereas insufficient acoustic activity may fail to provide therapeutically useful permeability enhancement [54,55].

5.3 Gene and Nucleic-Acid Delivery

Ultrasound can facilitate intracellular delivery of DNA, RNA, and other nucleic acids through sonoporation. Microbubble-mediated cavitation can transiently increase cell-membrane permeability and may therefore improve gene-transfer efficiency [26,27,36]. This strategy is particularly attractive because ultrasound provides spatial control that conventional systemic gene delivery lacks. However, achieving reproducible transfection while minimizing cellular injury remains a major challenge.

5.4 Localized Anti-Infective and Analgesic Therapy

Ultrasound-responsive depots and hydrogels can provide local treatment for infections and chronic wounds. Therapeutic compounds can remain immobilized or encapsulated until ultrasound is applied, allowing treatment intensity and timing to be adjusted according to clinical need [1,14,47]. Similar concepts could be used for local analgesic delivery, anti-inflammatory therapy, and postoperative treatment. The ability to activate a depot repeatedly could reduce the need for repeated injections.

6. Applications in Regenerative Medicine

6.1 Bone and Cartilage Regeneration

Ultrasound has long been investigated for bone healing. Low-intensity pulsed ultrasound can influence osteoblast activity, angiogenesis, extracellular matrix deposition, and signaling pathways involved in fracture repair [13,16,58–60]. Early clinical studies reported accelerated radiographic healing in selected fracture populations [59], although subsequent large randomized trials have produced mixed findings, highlighting the importance of patient selection and treatment context [60]. This distinction is important: ultrasound should not be assumed to improve every type of fracture or orthopedic outcome. A systematic review of randomized trials reported substantial heterogeneity among clinical studies [58]. Combining ultrasound with responsive scaffolds offers another strategy. Piezoelectric scaffolds can transform mechanical stimulation into electrical cues, potentially enhancing osteogenic signaling [10,49,50]. Ultrasound-responsive hydrogels can simultaneously provide growth factors and structural support.

6.2 Wound Healing

Chronic wounds are characterized by inflammation, impaired angiogenesis, infection, and defective extracellular matrix remodeling. Ultrasound can influence several of these

processes through mechanical stimulation and enhanced transport [1,9,17]. Ultrasound-responsive hydrogels and microcapsule-containing dressings can add controllable drug release to the intrinsic biological effects of ultrasound. Antibiotics, anti-inflammatory agents, growth factors, and extracellular-matrix-modulating molecules can potentially be delivered in response to treatment sessions [1,14,17].

6.3 Neural Regeneration

Ultrasound may influence neural repair through mechanotransduction, modulation of Schwann-cell activity, and stimulation of axonal growth [16]. Piezoelectric scaffolds provide a potential means of converting ultrasound into localized electrical signals, which may complement endogenous electrophysiological cues [10,49]. Future systems could combine neural stem cells or supportive cells with ultrasound-triggered neurotrophic-factor release, allowing therapeutic signals to be delivered during specific stages of regeneration.

6.4 Cardiovascular and Vascular Regeneration

Ultrasound-responsive microbubbles can modulate vascular permeability and have been explored for targeted cardiovascular delivery. In regenerative medicine, acoustic stimulation may influence endothelial cells and angiogenic signaling, while responsive carriers can deliver vascular growth factors or nucleic acids [36,49]. The combination of ultrasound, microbubbles, and targeted molecular payloads could therefore provide a means of coordinating angiogenesis with tissue repair.

6.5 Stem-Cell Modulation

Stem cells respond to mechanical and electrical cues in their microenvironment. Ultrasound can act as an externally controlled mechanical stimulus, while ultrasound-responsive hydrogels can release differentiation factors [14,18]. This creates an opportunity for "programmable" regenerative scaffolds in which ultrasound controls both the physical environment and the availability of soluble signals. Such platforms may be particularly valuable for tissues in which regeneration requires temporally coordinated signaling.

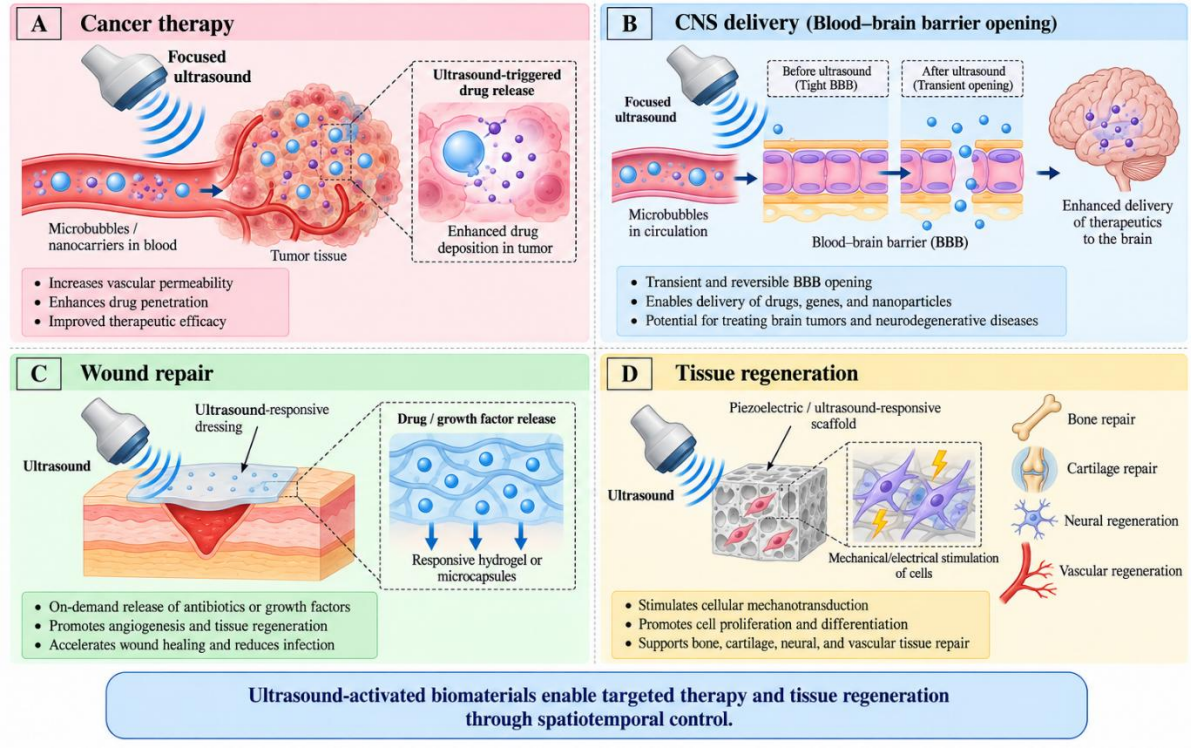

Figure 3. Representative biomedical applications.

(A) Cancer therapy: focused ultrasound activates microbubbles or nanocarriers within a tumor to enhance drug deposition. (B) CNS delivery: focused ultrasound and microbubbles transiently increase BBB permeability. (C)

Wound repair: ultrasound activates a responsive dressing to release antibiotics or growth factors. (D) Tissue regeneration: ultrasound stimulates piezoelectric scaffolds and cellular mechanotransduction to promote bone, cartilage, neural, or vascular repair.

7. Biosafety and Translational Challenges

The major advantage of ultrasound-responsive biomaterials—remote activation—is also a source of safety complexity. Acoustic exposure must be sufficiently strong to activate the biomaterial but sufficiently mild to avoid undesirable tissue effects. Thermal and mechanical bioeffects are therefore fundamental considerations [31–35]. Mechanical Index (MI) and Thermal Index (TI) provide standardized indicators for acoustic exposure, although these indices were primarily developed for diagnostic ultrasound and may not fully capture the complex exposure conditions associated with therapeutic biomaterials [34,35]. Experimental studies have demonstrated that microbubble-associated ultrasound can produce vascular effects under certain acoustic conditions, emphasizing the need for appropriate dose control [33]. Material-specific toxicity must also be considered. Lipids, polymers, perfluorocarbons, inorganic nanoparticles, piezoelectric ceramics, and sonosensitizers have different degradation, clearance, and immunological profiles. Nanomaterial accumulation and long-term degradation products require careful assessment.

Manufacturing is another major obstacle. Microbubbles and nanodroplets can be polydisperse, and small variations in size or shell composition can alter acoustic behavior [7,8,37]. Scale-up must therefore preserve not only chemical composition but also acoustic performance. Sterilization, storage stability, batch-to-batch reproducibility, payload loading, and release kinetics must be standardized before clinical implementation. These requirements are particularly demanding for combination systems involving a biomaterial, pharmaceutical payload, and ultrasound device. Regulatory classification can also be complicated because therapeutic ultrasound platforms may involve both device and drug components. Combination products can therefore require coordinated evaluation of material safety, pharmacology, acoustic performance, and device operation [6].

8. Clinical Translation and Regulatory Considerations

The translational pathway should begin with quantitative characterization of the acoustic response of the biomaterial. Important measurements include activation pressure, resonance behavior, release rate, temperature elevation, cavitation emissions, and repeated-use stability. *In vitro* testing should then examine cytotoxicity, membrane permeability, inflammatory responses, drug activity, and long-term material degradation. Three-dimensional tissue models may provide a more realistic representation of acoustic propagation than conventional monolayer cultures. Animal studies must evaluate biodistribution, clearance, immune responses, tissue injury, therapeutic efficacy, and the relationship between applied acoustic parameters and biological outcomes. Importantly, acoustic exposure should be reported using sufficiently detailed parameters to enable reproducibility. The transition to clinical studies requires scalable manufacturing and quality control. The uploaded source emphasizes that the development pathway progresses from material design and acoustic characterization through in vitro and animal testing, GMP-oriented scale-up, clinical trials, regulatory review, and clinical adoption. A further challenge is the absence of universal standards for reporting ultrasound-responsive biomaterials. Studies should consistently report frequency, pressure, intensity, pulse duration, duty cycle, treatment duration, transducer geometry, focal dimensions, and the presence or concentration of cavitation nuclei.

Standardized reporting would facilitate comparison among laboratories and accelerate regulatory assessment.

9. Future Perspectives

The next generation of ultrasound-activated biomaterials is likely to move beyond single-trigger systems toward adaptive, multimodal platforms. Integration of ultrasound with real-time imaging could allow clinicians to monitor bubble activity, temperature, material response, and therapeutic distribution during treatment. Artificial intelligence and computational acoustic modeling may further improve treatment personalization by accounting for patient-specific tissue geometry and acoustic heterogeneity. Closed-loop systems could adjust acoustic parameters according to real-time measurements of cavitation or temperature. Another important direction is multifunctionality. Future biomaterials may simultaneously carry drugs, genes, proteins, imaging agents, and regenerative signals. A single ultrasound exposure could then produce sequential biological effects—for example, vascular permeabilization followed by drug release and subsequent regenerative stimulation. Advanced manufacturing techniques, including 3D bioprinting, could create spatially heterogeneous scaffolds containing regions with different acoustic thresholds or piezoelectric properties. Biodegradable electroactive materials may provide wireless stimulation while avoiding permanent implanted electronics.

For CNS applications, improvements in acoustic focusing, cavitation monitoring, and individualized BBB-opening protocols could increase reproducibility and safety. Recent clinical literature indicates that FUS–microbubble BBB opening is progressing toward increasingly sophisticated therapeutic applications, although optimization of treatment parameters and long-term safety remains necessary [54–57]. Ultimately, successful translation will require convergence between materials science, ultrasound engineering, pharmacology, regenerative medicine, manufacturing, and regulatory science. The most clinically useful systems are likely to be those that demonstrate not only impressive acoustic responsiveness but also simple manufacturing, predictable pharmacokinetics, well-defined safety margins, and compatibility with existing clinical workflows.

10. Conclusions

Ultrasound-activated biomaterials provide a powerful platform for externally controlled drug delivery and regenerative medicine. By converting acoustic energy into mechanical, thermal, electrical, or chemical signals, these systems can regulate therapeutic release and cellular behavior with high spatial and temporal precision. Microbubbles and nanodroplets offer strong acoustic responsiveness; liposomes and polymeric carriers provide versatile payload delivery; hydrogels provide tissue-compatible depots; and piezoelectric materials provide a route toward wireless electro-mechanical stimulation. The principal opportunities include localized cancer therapy, BBB opening, gene delivery, wound treatment, bone and cartilage regeneration, neural repair, and stem-cell modulation. However, clinical translation requires careful control of cavitation and heating, standardized acoustic dosimetry, improved material reproducibility, long-term biosafety evaluation, scalable manufacturing, and appropriate regulatory strategies. The future of the field will likely depend on combining ultrasound-responsive biomaterials with multimodal imaging, adaptive acoustic control, intelligent drug-delivery architectures, and regenerative microenvironments. Such integration could transform ultrasound from a passive imaging or stimulation technology into a programmable therapeutic interface capable of controlling both drug disposition and tissue regeneration.

Author Contributions

Anil Kumar: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing Original Draft, Writing Review & Editing, Validation, Supervision, and Final Approval of the Manuscript.

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Data Availability Statement

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
US	Ultrasound
HIFU	High-Intensity Focused Ultrasound
LIPUS	Low-Intensity Pulsed Ultrasound
BBB	Blood–Brain Barrier
CNS	Central Nervous System
ROS	Reactive Oxygen Species
UCA	Ultrasound Contrast Agent
ARF	Acoustic Radiation Force
NPs	Nanoparticles
PLGA	Poly(lactic-co-glycolic acid)
PEG	Polyethylene Glycol
MRI	Magnetic Resonance Imaging
AI	Artificial Intelligence
GMP	Good Manufacturing Practice
FDA	U.S. Food and Drug Administration
CE	Conformité Européenne
MI	Mechanical Index
TI	Thermal Index
mTOR	Mechanistic Target of Rapamycin

ERK	Extracellular Signal-Regulated Kinase

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