

REVIEW

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Ultrasonic nanotechnology for the effective management of *Staphylococcus aureus* skin infections: an update

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Ultrasonic nanotechnology represents a groundbreaking advancement in the management of *Staphylococcus aureus* skin infections, addressing the significant limitations of conventional treatments. *S. aureus* poses substantial challenges, including antibiotic resistance and biofilm formation, necessitating novel and effective approaches. By harnessing the power of ultrasonic waves and nanostructures, this technology offers a precise mechanism to disrupt bacterial cells, enhancing antibiotic susceptibility and facilitating the eradication of bacterial colonies. This innovative approach not only improves treatment outcomes, but also offers a non-invasive and highly efficient alternative to traditional methods. Recent studies have demonstrated the remarkable efficacy of ultrasonic nanotechnology, showcasing its ability to revolutionize the treatment paradigm for *S. aureus* infections. Ongoing research is dedicated to refining treatment protocols, developing new nanostructures, and assessing clinical applicability, with a focus on overcoming challenges such as scalability and long-term effectiveness. This review provides a comprehensive overview of the current state of ultrasonic nanotechnology in combating *S. aureus* skin infections, detailing its mechanism of action, summarizing key research findings, and highlighting its superiority over conventional modalities. Accumulating evidence underscores its potential as a pivotal development in modern science and technology, promising significant advancements in infection management strategies. As research continues to evolve, the optimization of protocols, exploration of innovative applications, and translation into clinical practice are poised to further solidify the transformative impact of ultrasonic nanotechnology in the medical field.

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1. Introduction

Staphylococcus aureus, commonly known as “staph”, is a ubiquitous bacterium found on the skin and mucous membranes of humans and animals. While typically benign in these locations, it can lead to a spectrum of infections upon entry into the body through breaks in the skin, wounds, or abrasions. These infections range from minor skin ailments to severe, potentially life-threatening conditions.^{1,2} Managing *S. aureus* skin infections poses a persistent medical challenge due to several factors: a diverse range of infections: *S. aureus* can cause various skin conditions, from mild, superficial afflictions like folliculitis and impetigo to more serious infections such as cellulitis and abscesses;³ antibiotic resistance: the rise

of antibiotic-resistant strains, notably methicillin-resistant *Staphylococcus aureus* (MRSA), presents a significant hurdle in treating *S. aureus* infections. These strains exhibit resistance to multiple antibiotics, necessitating alternative, often more potent, treatment options.^{4,5}

Staphylococcus aureus possesses the capability to form biofilms, complex bacterial communities encased in a protective matrix, conferring heightened resistance to antibiotics, immune responses, and other antimicrobial agents, complicating treatment efforts.⁶ Despite treatment, *S. aureus* skin infections can persist or recur due to the bacterium's ability to establish deep-seated colonies within the body or evade immune surveillance.^{7,8} Moreover, *S. aureus* infections are highly transmissible through skin-to-skin contact, contaminated surfaces, and personal items, leading to outbreaks in various settings including healthcare facilities and communities.² In severe cases, *S. aureus* skin infections can lead to grave complications such as sepsis, necrotizing fasciitis, and endocarditis. Addressing these challenges necessitates a multi-faceted approach encompassing meticulous hygiene practices, timely wound management, judicious antibiotic usage, and

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robust infection control measures. The emergence of alternative modalities, including ultrasonic nanotechnology and novel antimicrobial agents, holds promise in confronting the escalating threat of antibiotic resistance. This review seeks to delineate recent advancements in the application of ultrasonic nanotechnology for the treatment and management of *S. aureus* skin infections, juxtaposing them with conventional treatment modalities and their limitations.

2. Existing methods of treatment and their challenges

Antimicrobial resistance (AMR) refers to the ability of microorganisms to withstand the effects of various antimicrobial agents, rendering previously effective drugs ineffective. Multidrug resistance (MDR) characterizes microorganism's resistance to multiple medications, posing significant challenges in clinical management.⁹ Microbes employ diverse resistance mechanisms, including acquired resistance from other species, genetic mutations, and innate resistance against specific antibiotics.⁹ The mechanisms underlying antibiotic resistance involve various strategies employed by bacteria to counteract the effects of antimicrobial agents. Various mechanisms contribute to bacterial resistance to antibiotics: bacterial enzymes can deactivate drugs, rendering them ineffective. For instance, MRSA demonstrates resistance through the reduction of drug absorption *via* decreased permeability of bacterial cells.¹⁰ Genetic mutations can induce structural modifications in drug targets, reducing their affinity for antibiotics. MRSA, for example, exhibits resistance attributed to altered penicillin-binding protein (PBP2a), which impedes the efficacy of β -lactam antibiotics like methicillin.¹¹ Additionally, some bacteria utilize efflux pumps to expel drugs from within the cell, thereby reducing intracellular drug concentrations.

While Gram-positive bacteria lack these pumps due to the absence of lipopolysaccharides in their outer membrane, Gram-negative bacteria employ efflux mechanisms alongside other resistance strategies.¹²

Biofilm formation presents a formidable challenge in the treatment of bacterial infections. Biofilms confer protection against host immune responses and substantially enhance bacterial resistance to antibiotics, often by orders of magnitude.¹³ Antibiotics such as imipenem and colistin demonstrate limited efficacy against biofilms, necessitating alternative treatment strategies.¹³ Biofilm-related infections, observed in pathogens like *Pseudomonas aeruginosa* and *S. aureus*, pose significant clinical hurdles due to their resilience and resistance to conventional therapies.⁶ Diagnosing biofilm infections often requires specialized microbiological techniques. Sonication of indwelling devices followed by 16S rRNA sequencing offers reliable identification of biofilm-associated organisms.¹⁴ Additionally, biomarkers such as blood leukocyte count, C-reactive protein, interleukin-6, and procalcitonin levels may aid in biofilm detection.¹⁴ Fluorescence *in situ* hybridization (FISH), employing labelled DNA or peptide nucleic acid probes, proves valuable in diagnosing biofilm infections, particularly in conditions like cystic fibrosis and chronic wounds.¹⁴

3. Emergence of ultrasonic nanotechnology

The application of nanomaterials is witnessing a significant increase across various industries, particularly in the medical sector.¹⁵ Fig. 1 highlights the essential properties and uses of ultrasonic nanoparticles. It's pertinent to acknowledge that various nanomaterials can undergo ultrasonic treatment, catalyzing significant advancements in medicine and scientific



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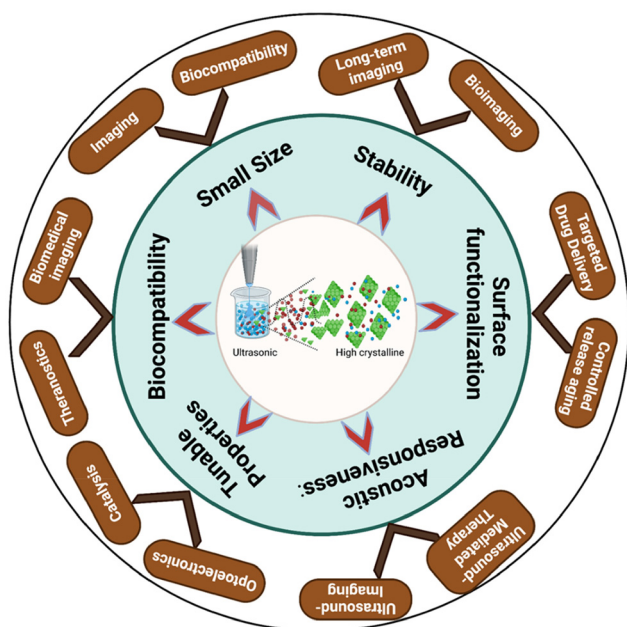


Fig. 1 Important properties and applications of ultrasonic nanoparticles.

exploration. However, it's essential to note that only a select number of nano-proteins possess the capability to undergo ultrasonic treatment, facilitating the hydrolysis and elimination of scales from amorphous regions. This approach presents advantages such as reduced treatment duration and environmental compatibility.¹⁶

Disrupting bacterial cell walls offers a multifaceted approach in combating infections, encompassing a spectrum of clinical techniques. These include chemical antiseptics and disinfectants, antibiotics, antimicrobial peptides, bacteriophages, photodynamic therapy, electroporation, chemotherapy, immunotherapy, and ultrasound therapy. Antiseptics

and disinfectants serve as primary defense mechanisms against pathogens. While disinfectants inhibit pathogens on inanimate surfaces, antiseptics target skin microbes to mitigate infections. Notably, certain disinfectant products exhibit superior efficacy, such as hydrogen peroxide and sodium hypochlorite, compared to quaternary ammonium chlorides.¹⁷ High-quality antiseptics and disinfectants can reduce minimum bactericidal concentrations and microbial growth.¹⁸ Commonly used antiseptics in dermatology include chlorhexidine, povidone-iodine, chloroxylenol, isopropyl alcohol, hexachlorophene, benzalkonium chloride, and hydrogen peroxide.¹⁹ Antiseptics penetrate microorganisms, inhibiting essential cellular processes and leading to cell death.

Systemic antibiotics, derived from microbial sources, play a pivotal role in infection control. Different microbes produce antibiotics that target pathogens through distinct mechanisms. However, the overuse and misuse of antibiotics pose long-term health risks.²⁰ Antimicrobial peptides (AMPs), also known as host defense peptides (HDPs), exhibit a broad spectrum of activity against bacteria, fungi, and viruses. AMPs disrupt microbial cell membranes, inhibiting essential cellular processes and modulating immune responses.^{21,22} Their small size, cationic nature, and amphipathic structures contribute to their efficacy against pathogens.²³ Ultrasonic nanotechnology represents a frontier in medical, electronics, and materials science. This review will explore the historical context, key contributors, and impact of non-invasive ultrasonic nanotechnology approaches.²⁴ Additionally, it will present a balanced analysis of the positive and negative aspects, as well as potential future breakthroughs in non-invasive ultrasonic nanotechnology. Ultrasound technology has revolutionized medical imaging, drug delivery, and tissue engineering, with ongoing research exploring its potential for focused medication delivery to the brain.^{25,26} Nanoscale ultrasound may offer a non-invasive method to penetrate the blood-brain barrier, enabling targeted drug delivery to treat neurological disorders.



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Table 1 Recent Advances in ultrasonic nanotechnology for the effective management of *S. aureus* skin infections

Recent advances	Principle	Application	Ref.
Photoacoustic imaging	Infection models employ photothermal ablation and photoacoustic imaging	Biofilms and infected tissues are visualized	91
Piezoelectric nanostructured	Enhance the reactive oxygen species (ROS) at the surface	Immunoregulation and effective antibacterial activity	92
MoS ₂ and Cu ₂ O heterostructures in piezoelectric materials	Sonodynamic generate reactive oxygen when exposed to exogenous ultrasonic (US) waves	Excellent biocompatibility and 99.85% antibacterial activity	93
Sodium molybdenum bronze nanoplatfrom (SMB-NPs)	A second near-infrared (NIR-II) photothermal action generates abundant oxygen vacancies	Enhanced antibacterial efficacy	94
Triboelectric nanogenerator (TENG)	Ultrasound (US) drives an implant for electrical stimulation	Remove microorganisms from deep tissues	95
Farnesol-containing nanoparticles	High-intensity ultrasound to create new nanoparticles (NPs)	The study found strong antiviral and anti-inflammatory cytokines in a 3D skin tissue model	96
Silver nanoparticles	Ultrasound-assisted reverse micelles method	The drug has a strong inhibitory effect against methicillin-resistant <i>Staphylococcus aureus</i>	97
Thyme essential oil nanoemulsions (TEON)	Ultrasounds decreased membrane hydrophobicity	The integrated technology enhances <i>S. aureus</i> inactivation through its synergistic mechanisms	98
Polymeric nanoparticles (PNPs)	Ultrasound with polymeric nanoparticles (PNPs)	It eradicates and disrupts bacterial biofilms, rapidly increasing PNP penetration	68
Bimetallic nanozymes	The activity of oxidase and peroxidase replicates the functions of actual enzymes	The drug has a strong inhibitory effect against methicillin-resistant <i>S. aureus</i>	99
ZnO nanoparticles	A high-power US forms a cavitation zone between two zinc electrodes	The antibacterial effect is long-lasting and starts quickly	100
Core-shell structured upconversion nanoparticles (CS-UCNPs)	Fluorescence-based aptamer biosensor	The biosensor boasts rapid detection and increased sensitivity	101
Shell-core-structured IR780-based PLGA nanoparticles	Sonodynamic therapy (SDT)	Deep tissue penetration and noninvasiveness	102
Polymer nanoparticles	Enhanced by mild hyperthermia	Treat infectious skin lesions and chronic wounds, including diabetic foot ulcers	103
Silver nanoparticles	AgNPs and low-frequency USs collaborate	Skin infection microorganisms are eliminated, and new tissue with full epithelization is created	104

4. Advances in ultrasonic nanotechnology research

Recent advances in ultrasonic nanotechnology research have propelled the field forward in several key areas. Table 1 lists the recent advances in ultrasonic nanotechnology for the effective management of *S. aureus* skin infections. Notable progress has been achieved in ultrasonic imaging resolution, with

techniques such as photoacoustic imaging enabling high-resolution visualization of biological structures and nanoparticles at the nanoscale.^{27,28} Therapeutic applications have also seen significant development, including targeted drug delivery facilitated by nanoscale drug carriers that can be guided using ultrasound for precise delivery to specific sites within the body.^{29,30} Additionally, ultrasonic techniques have been instrumental in synthesizing and manipulating nanoparticles with tailored properties, leading to advancements in diverse applications such as catalysis,³¹ sensing,³² and biomedicine.³³ Nano-enhanced ultrasound contrast agents, including nanobubbles and nanodroplets, have shown promise in improving imaging contrast and sensitivity for disease detection and monitoring. The emergence of theranostic nanoparticles, which integrate diagnostic and therapeutic functionalities, represents a significant advancement in personalized medicine approaches. Furthermore, research efforts have focused on understanding the biological effects of ultrasound at the nanoscale, guiding the development of safe and effective ultrasonic technologies for biomedical applications.^{34,35} Nanostructured materials have also been explored for ultrasonic sensing applications, offering enhanced sensitivity and compatibility with miniaturized devices for various healthcare, environmental, and industrial applications. These advancements collectively contribute to the continued growth and innovation in ultrasonic nanotechnology, with implications for improved diagnostics, therapy, imaging, and sensing across diverse fields of science and technology.



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At the nanoscale level, ultrasonic waves offer precise and non-invasive therapeutic interventions, rendering this domain a captivating area for further exploration and development. Current research endeavors primarily aim to optimize treatment strategies leveraging ultrasonic nanotechnology in healthcare settings.^{36,37} Pioneering contributions from interdisciplinary experts, such as doctors, scientists, and bioengineers, have significantly propelled the advancement of nanoscale ultrasound technology in medicine. Notably, nanoparticle-based approaches have revolutionized ultrasonography, particularly in the context of cancer care.³⁸ Dr Kullervo Hynynen, from the Department of Medical Biophysics at the University of Toronto, stands out as one of the early adopters, pioneering the application of focused ultrasound for non-surgical treatment of nerve-related and other health issues.³⁹ Further innovations aim to utilize ultrasound pulses to target specific brain regions, offering promising avenues for conditions like Parkinson's disease.

Ongoing research in ultrasonic nanotechnology has significantly impacted medical practice, yielding reduced complications during invasive procedures, improved patient outcomes, and enhanced quality of life, especially for individuals with complex or incurable diseases.⁴⁰ The ability to precisely target cells or tissues with ultrasonic waves enables the formulation of personalized treatment plans tailored to optimize efficacy while minimizing adverse effects. Moreover, ongoing investigations in this field have expanded our understanding of cellular and molecular processes through novel applications of ultrasound at the nanoscale level.^{41,42} This deeper insight into disease pathophysiology facilitates the identification of potential therapeutic targets, paving the way for the development of innovative treatment strategies. Ongoing research in ultrasonic nanotechnology holds tremendous promise for revolutionizing medical interventions by enabling precise, non-

invasive, and personalized treatment approaches. The collaborative efforts of multidisciplinary teams continue to drive advancements in this field, offering hope for improved patient care and enhanced therapeutic outcomes across various medical domains,^{43,44} likely investigated the ROS-mediated mechanisms of action of ultrasonic nanotechnology in different experimental models or contexts, providing insights into the efficacy and potential applications of sonodynamic therapy for various biomedical purposes. Their findings contribute to the understanding of how ultrasonic waves combined with nanomaterials can be harnessed to induce ROS generation and exploit the resulting cytotoxic effects for therapeutic purposes, such as cancer treatment or antimicrobial therapy (Fig. 2).

Ultrasonic nanotechnology represents a promising advancement for managing *S. aureus* skin infections due to its ability to produce ROS and thermal effects at localized sites. However, ensuring the biosafety of this technology is crucial for clinical application. Operating at frequencies above 20 kHz, ultrasonic nanotechnology interacts with tissues and nanoparticles in a controlled manner, minimizing damage to surrounding healthy tissues.⁴⁵ Studies indicate that at therapeutic doses, it does not induce significant cytotoxicity or genotoxicity.^{46,47} Long-term animal studies have corroborated the absence of adverse effects, suggesting its potential safety for human applications.⁴⁸ Continuous monitoring and evaluation remain essential as this technology progresses towards clinical trials. The controlled production of ROS and thermal effects ensures minimal damage to healthy tissues, supporting the non-cytotoxic and non-genotoxic nature of ultrasonic nanotechnology at therapeutic doses.⁴⁹ Although long-term animal studies reinforce its potential safety, ongoing assessment will be critical as it advances towards clinical use.

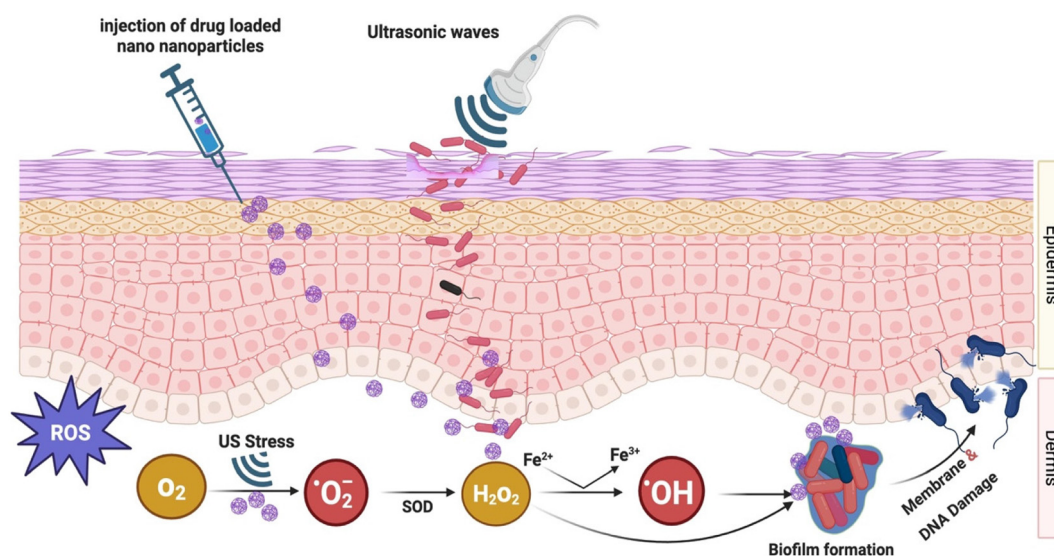


Fig. 2 Mechanism of action of ROS in ultrasonic nanotechnology.

5. Impact of innovative nanostructures

Nanomaterials have become ubiquitous across numerous industries, particularly in healthcare, where their unique properties offer promising avenues for innovation.⁵⁰ These materials, synthesized through various methods, are typically categorized as hard or soft based on their composition, size, and shape. In medicine, nanostructures have revolutionized disease therapy by facilitating targeted drug delivery systems. This innovative approach allows precise drug administration to specific body regions, thereby reducing adverse effects and enhancing therapeutic efficacy.

In the electronics industry, the discovery and utilization of nanoscale materials have resulted in the development of smaller, faster, and more efficient devices. This advancement has led to notable progress in computing, telecommunications, and other electronic technologies. Furthermore, nanostructures have found applications in energy-related fields, contributing to the creation of more efficient solar cells, batteries, and catalytic systems. These developments are pivotal in accelerating the transition to renewable energy sources. Key figures in the field, such as Prof. Chad Mirkin from Northwestern University, have significantly contributed to the advancement of nanoscale materials for diverse applications. Mirkin's development of Dip-Pen Nanolithography has revolutionized nanotechnology by enabling precise patterning of materials on surfaces, leading to breakthroughs in biosensing and drug delivery.⁵¹ Similarly, Prof. Angela Belcher from the Massachusetts Institute of Technology has made substantial contributions to nanotechnology by synthesizing and assembling nanoscale materials for use in energy, electronics, and medicine.⁵² Despite the myriad of benefits offered by novel nanostructures, it is essential to consider potential downsides. One of the most significant concerns pertains to the environmental and health implications of nanoscale materials. As their prevalence increases in industrial and consumer goods, it is imperative to ensure that their production and usage do not pose risks to the environment or human health. Additionally, the societal impacts of nanotechnology warrant careful consideration, highlighting the importance of ethical and regulatory frameworks in guiding its responsible development and deployment.

6. Evaluating clinical feasibility: addressing scalability and long-term efficacy challenges

The notion of clinical viability has undergone significant evolution in tandem with the increasing complexity of healthcare interventions and the growing emphasis on evidence-based practice.^{53,54} In the early stages of medicine, clinical viability often relied on individual practitioners' experience and intuition, with minimal emphasis on standardized evaluation methodologies. However, the assessment of clinical viability for ultrasonic nanotechnology necessitates thorough evalu-

ation of its effectiveness and safety for medicinal applications.⁵⁵ This evaluation encompasses determining its capability to deliver therapeutic drugs or imaging contrast agents to specific targets, such as tumors or diseased tissues, while mitigating off-target effects.⁵⁶ Moreover, factors like biocompatibility, stability, and scalability are pivotal considerations in determining the feasibility of implementing ultrasound nanotechnology in clinical settings.⁵⁷

Clinical research and trials play a crucial role in evaluating the efficacy and safety of ultrasound-based nanotechnologies in real-world scenarios, ultimately shaping their potential for widespread clinical application in the detection and treatment of various medical conditions.⁵⁸ Several notable figures have made significant contributions to analyzing clinical viability and addressing scalability and long-term efficacy challenges. For instance, the development and application of diverse nanomaterials for more effective cancer ultrasound therapies have overcome inherent limitations associated with traditional ultrasound microbubble contrast agents. Substantial progress has been made in targeted tumor therapy using nanoparticulate theranostic drugs and ultrasound molecular imaging.⁵⁹ Current research efforts are focused on anticancer drug delivery using nanoscale drug delivery systems (DDSs), capitalizing on ultrasound's potential to influence cellular behavior and drug delivery mechanisms.⁶⁰ Ultrasonic nanotechnology enables more sensitive and specific tissue imaging, facilitating early disease detection and accurate diagnosis of conditions like cancer, cardiovascular disorders, and neurological diseases.⁶¹ Moreover, ultrasound-mediated drug delivery utilizing nanotechnology allows efficient transport of therapeutic agents across biological barriers, such as the blood-brain barrier or tumor endothelium, thereby expanding treatment possibilities for previously untreatable conditions.²⁶ By leveraging nanotechnology, physicians can perform minimally invasive treatments with precision and accuracy through ultrasound-guided interventions. Reduced reliance on standard surgical procedures translates to quicker recovery, decreased morbidity, and enhanced patient comfort.⁶² However, challenges persist, particularly in evaluating long-term effectiveness, especially for chronic and multifactorial conditions. Additionally, ensuring the scalability of clinical interventions across diverse healthcare settings poses logistical and resource challenges that may impede widespread implementation.

7. Mechanism of action of ultrasonic waves

The mechanism of action involving ultrasonic waves revolves around the generation of vibrations at frequencies higher than 20 000 Hz, with the power of ultrasonic waves being crucial for optimizing their performance across various applications.⁶³ These waves, which are sound waves beyond the audible range of human hearing, possess unique properties applicable in diverse fields such as food processing, energy harvesting, material treatment, structural health monitoring, and

research. Ultrasonic waves propagate through a mechanism involving sound wave propagation. Essentially, these waves are generated using two methods, namely, electric and magnetic.⁶⁴ In the realm of ultrasound nanomedicine, these waves stimulate bacterial surfaces, inducing modifications. As bacteria move, they can generate ROS, leading to the eradication of *S. aureus* and the suppression of genes responsible for biofilm formation.⁶⁵ Antimicrobial sonodynamic treatment (aSDT) based on ultrasound irradiation, utilizing nanosonosensitizers to produce ROS and exert antimicrobial effects without antibiotics, has also been investigated.⁶⁶ For instance, Au@Cu₂O hybrid nanocubes have been employed as novel antibiotic sonosensitizers, demonstrating the efficacy of sonodynamic treatment (SDT) utilizing ultrasound (US) against bacteria, particularly *S. aureus*.⁶⁷

Recent research outcomes have highlighted the effectiveness of ultrasonic waves in eradicating bacterial biofilms and enhancing treatment efficacy under various conditions. Combination treatments, such as ultrasound and antimicrobial polymeric nanoparticles (PNPs), have proven effective in eradicating bacterial biofilms, with outcomes dependent on factors like PNP concentration and ultrasound duration.⁶⁸ Moreover, the enhancement of ultrasound efficacy through narrow-band radiofrequency (RF) signals has been explored, demonstrating high efficiency signal measurement,

calibration, and control system implementation.⁶⁹ Additionally, ultrasonic treatment has shown effectiveness in wastewater purification and improving antimicrobial activity in biological treatment processes.⁷⁰ Even in challenging scenarios like waste livestock blood solubilization for protein treatment, ultrasonic waves have been effective.⁷¹

Nanostructures play a pivotal role in facilitating precision targeting in bacterial cell interactions by modulating the interaction between bacterial cells and their environment. Bacteria, characterized by specialized structures like the bacterial cell membrane, engage in interactions crucial for both harmful and symbiotic purposes.⁷² Nanostructures offer diverse properties that impact physical, electrical, chemical, biological, and optoelectrical aspects, enhancing scientific and engineering endeavors at the nanoscale level.⁷³ Various types of nanostructures, including nanowires, nanofibers, nanotubes, nanobelts, and nanoparticles, have unique properties that influence bacterial cell interactions.⁷⁴ Nanostructured surfaces can facilitate bacterial cell attachment, affecting bacterial sensing and adhesion to material surfaces.⁷⁵ These surfaces alter surface charge, cell stiffness, and bacterial motility, leading to emergent reactions such as cell wall breakage and death.^{76,77} Intense shear and mechanical processes generated during the burst of cavitation bubbles may damage the cell wall of bacterial membranes (Fig. 3). This disruption of bacterial integrity

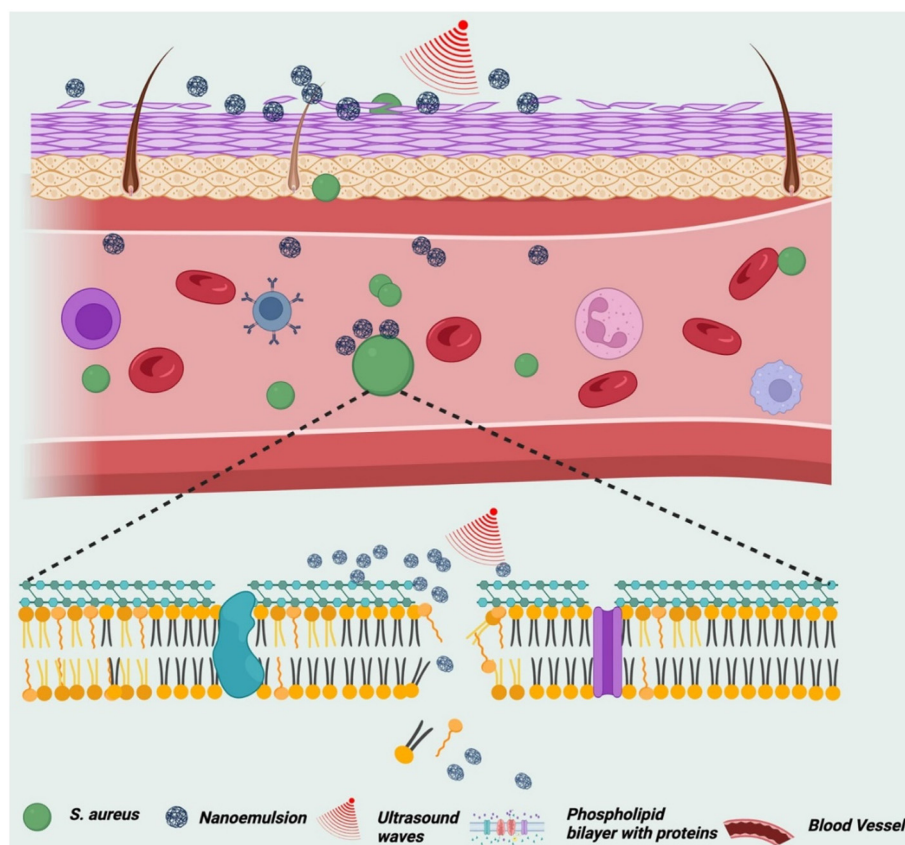


Fig. 3 Impact of ultrasonic waves on bacterial membranes.

can lead to various effects, ultimately contributing to the eradication of bacterial populations.

Furthermore, ultrasonic nanotechnology offers significant advantages over other ROS-based antibacterial technologies like photodynamic therapy (PDT) and electrodynamic therapy (EDT).^{78,79} Unlike PDT, which is limited by light penetration and tissue depth, ultrasonic waves can penetrate deeper into tissues for more effective treatment of infections beneath the skin surface.⁸⁰ Additionally, ultrasonic nanotechnology targets bacterial cells precisely without needing external photosensitizers, reducing the risk of side effects from photosensitizer accumulation.⁸¹ Compared to EDT, which involves electrical currents causing discomfort and potential tissue damage, ultrasonic nanotechnology is non-invasive and painless, enhancing patient comfort and compliance. Integrating ultrasonic nanotechnology in antibacterial strategies and medical treatments demonstrates its transformative potential, enabling more effective, targeted, and non-invasive treatments. This advancement opens new research and application avenues, improving patient outcomes and reducing conventional treatment risks. Addressing challenges like optimizing nanoparticle synthesis, ensuring safety, and understanding long-term effects requires collaborative efforts from researchers, clinicians, and industry stakeholders. The future of medicine and materials science lies in the convergence of nanotechnology and ultrasound, promising a new era of precision treatments and innovative solutions, deepening our understanding of the nanoscale world, and inspiring technological advancements to improve human health and well-being.

8. Recent research outcomes and comparative advantages over traditional approaches

Recent advancements in ultrasonic nanotechnology have demonstrated significant potential in improving the effectiveness of antibacterial strategies. Fig. 4 illustrates the enhancement of antibacterial nanostrategies through the addition of ultrasound, magnetic fields, light, and ionizing radiation. These nanoparticles (NPs) possess unique features such as greater contact with bacteria due to their smaller size and improved surface area-to-mass ratio. Alterations in the size, shape, and chemical composition of NPs can further enhance their potency. Various types of NPs, including metallic, chemical, biomolecular, radio, and antibody-modified, can employ diverse mechanisms to kill bacteria.⁸² Fig. 5 depicts the synthesis of FSL nanoparticles with and without the use of ultrasound, alongside their shape characterization *via* scanning electron microscopy (SEM). This figure also includes SEM images showing the efficacy of NP-treated bacterial biofilm at various concentrations, time-killing kinetics, and live/dead microscopic visualization. Superimposed green and red fluorescence images at different concentrations highlight the substantial statistical differences in biofilm reduction potential of FSL NPs, even at the lowest concentration, effectively reducing both mature biofilm and empty NPs.⁸³

Ultrasonic waves have gained prominence in medical treatments and their significance extends to neurosurgery, vestibular surgery, and physiotherapy, where they provide valuable

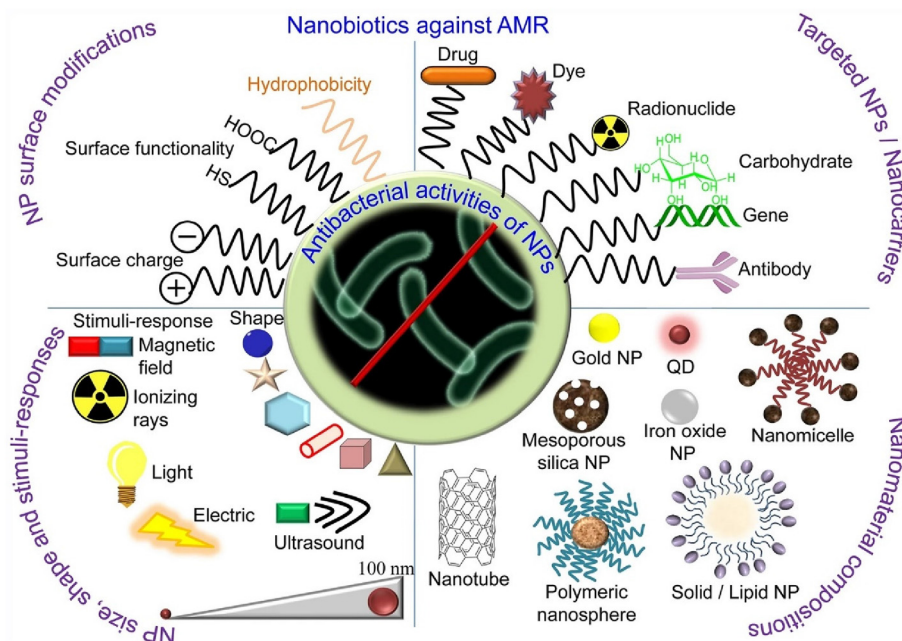


Fig. 4 Enhancement strategies for antibacterial nanoparticles using ultrasound, magnetic fields, light, and ionizing radiation. Reproduced from ref. 82.

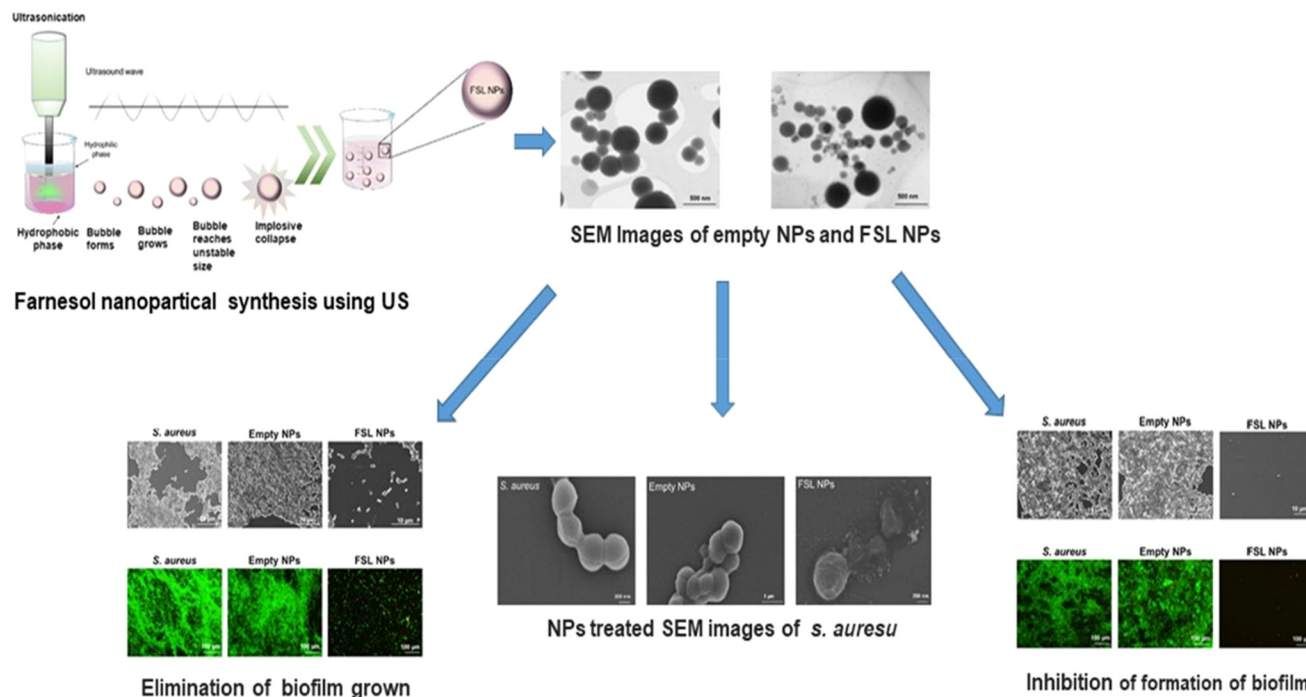


Fig. 5 Synthesis, shape characterization, and efficacy assessment of fluorescent silica-lipid hybrid nanoparticles (FSL NPs) with and without ultrasound. SEM images of nanoparticle-treated *S. aureus* and inhibition of biofilm formation. Reproduced from ref. 83.

information about tissue conditions and enable non-contact treatments. Ultrasonic waves offer non-invasive treatment options that minimize the need for surgical procedures, precisely target specific areas, and promote faster healing and recovery due to their gentle nature. These treatments are often painless, reducing the risk of infection since they do not involve incisions or invasive techniques. Ultrasonic technology is safe and effective for various medical conditions. Precision methods, which use automation and new technologies for high targeting accuracy, reliability, and specificity, are exemplified in precision medicine.^{84,85} These approaches consider the unique qualities of each patient and are highly efficient, adaptable, and data-driven, although they may incur higher initial costs. In contrast, traditional procedures rely on well-established technologies and past experiences, which, while having lower starting costs, may be less resource-efficient over time. Non-invasive ultrasonic nanotechnology techniques contribute to nanotechnology advancements by offering precise control, improved imaging, and reduced invasiveness in manipulating and studying nanoscale phenomena.⁸⁶ Examples of non-invasive techniques include ultrasound imaging,⁸⁷ ultrasonic drug delivery,⁸⁸ acoustic tweezers, focused ultrasound therapy, nanoparticle characterization using acoustic spectroscopy, and ultrasound-mediated biosensing.⁸⁹ These methods minimize potential harm to living organisms, making them an attractive option for various applications.

The integration of ultrasonic nanotechnology in antibacterial strategies and medical treatments highlights the transformative potential of this approach. Leveraging the unique properties of nanoparticles and the precision of ultrasonic waves

allows for the development of more effective, targeted, and non-invasive treatments. Advancements in this field open new avenues for research and application, particularly in improving patient outcomes and reducing the risks associated with conventional treatments. Addressing challenges such as optimizing nanoparticle synthesis, ensuring safety and biocompatibility, and understanding the long-term effects of ultrasonic treatments is crucial. Collaborative efforts between researchers, clinicians, and industry stakeholders are essential in overcoming these hurdles and unlocking the full potential of ultrasonic nanotechnology. The future of medicine and materials science lies in the convergence of nanotechnology and ultrasound, promising a new era of precision treatments and innovative solutions. Pushing the boundaries of what is possible will pave the way for groundbreaking advancements that will shape the future of healthcare and beyond. This scientific journey deepens our understanding of the nanoscale world and inspires us to reimagine the possibilities of technology in improving human health and well-being. Fig. 6 illustrates the confirmation of nanoparticle mixtures for safe and effective ultrasonic drug uncaging. It highlights dose-response relationships and particle kinetics in living systems, providing crucial insights into how nanoparticles can be used to precisely control drug release within the body. This figure demonstrates the meticulous processes involved in ensuring the safety and efficacy of ultrasonic nanotechnology, showcasing its potential to revolutionize drug delivery and therapeutic strategies.

Furthermore, transitioning from preclinical research to clinical application involves several critical steps, including optimizing treatment parameters, large-scale production of

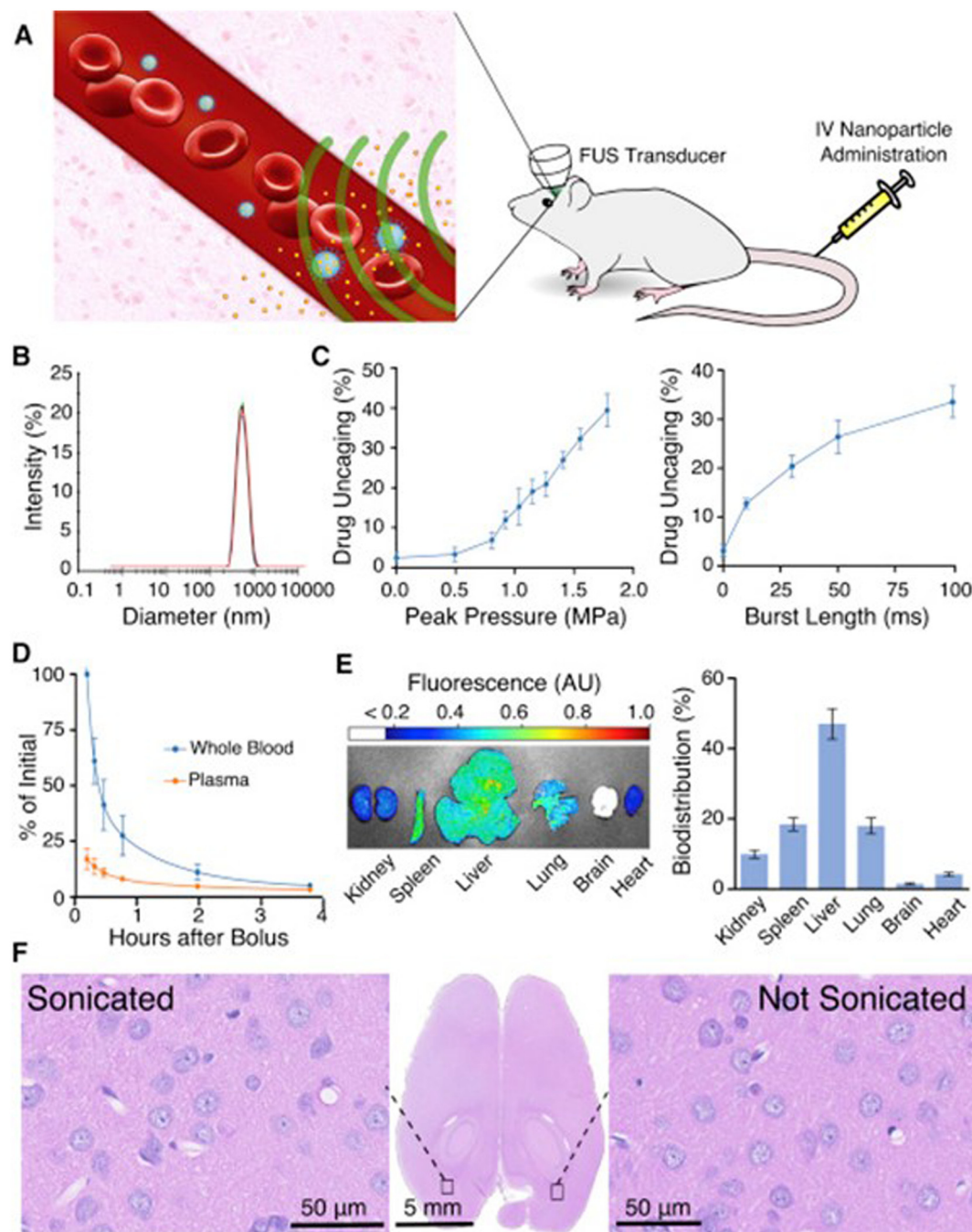


Fig. 6 (A) The image illustrates the drug release from nanoparticles, which diffuses into the bloodstream and brain through focused ultrasound, demonstrating the effective distribution of nanoparticles in the blood. (B) The nanoparticle dynamic light scattering results show a monodisperse peak, indicating nanoscale material. (C) The image demonstrates *in vitro* drug uncaging efficacy using focused sonication on propofol-loaded nanoparticles, assessing the amount of uncaged drug partitioned into an organic solvent. (D) The image represents the kinetics of encapsulated nanoparticles in whole blood and plasma, with curves fitting a double-exponential model to the data. (E) The image shows fluorescence detected in six organs, indicating nanoparticle biodistribution in a single animal. (F) The image depicts a transverse section of a rat's brain, stained with hematoxylin and eosin, following the administration of propofol-loaded nanoparticles and exposure to focused sonication. Reproduced from ref. 90 with permission from Elsevier Copyright 2024.

nanomaterials, and conducting rigorous clinical trials to establish efficacy and safety in human patients. Promising pre-clinical results have demonstrated the potential of ultrasonic nanotechnology to effectively manage *S. aureus* skin infections,

particularly in overcoming antibiotic resistance and biofilm-associated challenges. Clinical trials are underway to evaluate therapeutic outcomes, patient safety, and long-term effects of ultrasonic nanotechnology in diverse patient populations.

Successful translation into clinical practice could revolutionize infection management, offering a non-invasive, highly effective, and safe treatment modality.

9. Conclusion and future prospective

This updated review study has clarified the potential of ultrasonic nanotechnology as an effective approach for managing *S. aureus* skin infections. The findings underscore the importance of continued research and development in this field to fully exploit the benefits of this technology. Future research should focus on the development of novel nanomaterials with specific targeting capabilities, improved stability, and enhanced antimicrobial properties. Advanced materials such as graphene oxide, carbon nanotubes, and metal-organic frameworks hold promise for creating more effective ultrasonic agents. Understanding the precise mechanisms by which ultrasonic waves interact with nanomaterials and bacterial cells is crucial, necessitating the use of advanced imaging and spectroscopic techniques to elucidate these mechanisms at the molecular level. Furthermore, optimizing the parameters of ultrasonic treatment, including frequency, intensity, and duration, is essential for maximizing therapeutic outcomes. Identifying the optimal conditions that ensure maximum bacterial eradication while minimizing potential damage to surrounding healthy tissues will be a key focus.

Exploring the synergistic effects of combining ultrasonic nanotechnology with other therapeutic modalities, such as antibiotics, photothermal therapy, or immunotherapy, could lead to more effective and comprehensive treatment strategies. Bridging the gap between laboratory research and clinical application is a critical step for the successful implementation of ultrasonic nanotechnology. Future efforts should focus on conducting preclinical studies and clinical trials to evaluate the safety, efficacy, and practicality of this technology in real-world settings. Advances in ultrasound technology, such as the development of portable and wearable ultrasound devices, could revolutionize the management of *S. aureus* skin infections by creating user-friendly and accessible treatment options for patients. The integration of ultrasonic nanotechnology into clinical practice has the potential to significantly improve the management of *S. aureus* skin infections. This technology offers a non-invasive, targeted, and efficient treatment modality that could reduce the reliance on conventional antibiotics and mitigate the risk of antibiotic resistance. Demonstrating the clinical benefits of this technology through rigorous clinical studies and cost-benefit analyses will be essential for its widespread adoption. By addressing these challenges and exploring the outlined future research directions, ultrasonic nanotechnology can pave the way for innovative and effective treatments of *S. aureus* skin infections.

Future research trends in ultrasonic nanotechnology for managing *S. aureus* skin infections suggest several promising directions. The development of advanced nanomaterials will likely focus on enhancing biocompatibility and functional-

ization to target bacterial cells more precisely. Understanding the interaction mechanisms between ultrasonic waves, nanomaterials, and bacterial cells in detail at the molecular level will provide insights into improving the treatment efficiency. Additionally, optimizing the ultrasonic treatment parameters to achieve maximum efficacy with minimal side effects will be a crucial area of investigation. Combining ultrasonic nanotechnology with existing therapeutic methods, such as antibiotics and immunotherapies, could offer a multi-faceted approach for tackling infections. The advancement of portable and wearable ultrasound devices promises to make this technology more accessible and practical for clinical use, potentially transforming standard care practices for bacterial skin infections. The anticipated impact on clinical practices includes a shift towards more targeted and efficient treatments that reduce the risk of antibiotic resistance, ultimately leading to better patient outcomes and more sustainable infection management strategies.

Author contributions

NT, BAL, LB: Investigation; validation; writing – original draft. VB: Resources; visualization; writing – review & editing. YJK: Reviewing & editing; resources; supervision; project administration; funding acquisition.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare that they do not have conflicts of interest.

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