Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 22 March 2026
Revised 28 April 2026
Accepted 18 May 2026

Natural Resources for Human Health 2026, Vol. 6 (2s): 837–848

KEYWORDS:
Photoacoustic imaging, nanoparticles, dental caries, early diagnosis, contrast agents, nanotechnology, optical imaging, dental diagnostics

Integration Of Nanoparticles with Photoacoustic Imaging in Caries Diagnostics: A Comprehensive Review

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ABSTRACT: Dental caries remains one of the most prevalent chronic diseases worldwide, affecting populations across all age groups and socioeconomic strata. Early detection of carious lesions is crucial for implementing minimally invasive treatment strategies and preserving tooth structure. Traditional diagnostic methods, including visual-tactile examination and radiography, often fail to detect incipient lesions in their earliest stages. Photoacoustic imaging (PAI) has emerged as a promising non-invasive diagnostic modality that combines the advantages of optical contrast with ultrasonic resolution. The integration of nanoparticles as contrast agents with PAI technology represents a paradigm shift in caries diagnostics, offering enhanced sensitivity, specificity, and depth penetration. This comprehensive review examines the fundamental principles of photoacoustic imaging, explores various types of nanoparticles employed as contrast agents, discusses their synthesis and functionalization strategies, and evaluates their clinical applications in early caries detection. Furthermore, this paper addresses the biocompatibility considerations, regulatory challenges, and future perspectives of this innovative diagnostic approach. The integration of nanotechnology with photoacoustic imaging holds tremendous potential for revolutionizing dental diagnostics and enabling personalized preventive care strategies.

1. INTRODUCTION

Dental caries is a multifactorial biofilm-mediated disease characterized by the localized destruction of susceptible dental hard tissues through acidogenic bacteria (Pitts et al., 2017). The World Health Organization estimates that dental caries

affects nearly 3.5 billion people globally, representing a significant public health burden (Kassebaum et al., 2015). The pathogenesis of dental caries involves a dynamic process of demineralization and remineralization, where the balance tips toward mineral loss when cariogenic bacteria metabolize fermentable carbohydrates, producing organic acids that dissolve hydroxyapatite crystals in enamel and dentin (Fejerskov et al., 2015).

Early detection of carious lesions at the incipient stage, when remineralization is still possible, is paramount for implementing preventive and minimally invasive treatment strategies (Fried et al., 2005). However, conventional diagnostic methods have inherent limitations. Visual-tactile examination lacks sensitivity for detecting non-cavitated lesions and interproximal caries, while bitewing radiography exposes patients to ionizing radiation and typically detects lesions only after significant mineral loss has occurred (Bader and Shugars, 2004). Furthermore, these traditional methods provide limited information about lesion activity and depth, which are critical parameters for clinical decision-making.

The limitations of conventional diagnostic techniques have stimulated research into novel imaging modalities that can detect carious lesions at earlier stages with greater accuracy. Among these emerging technologies, photoacoustic imaging (PAI) has garnered considerable attention due to its unique ability to provide high-resolution structural and functional information at depths beyond the reach of pure optical imaging techniques (Wang and Yao, 2016). PAI operates on the photoacoustic effect, wherein tissues absorb pulsed laser light and undergo thermoelastic expansion, generating acoustic waves that can be detected by ultrasound transducers (Beard, 2011).

The integration of nanoparticles as contrast agents with PAI technology represents a transformative approach to caries diagnostics. Nanoparticles possess unique optical, magnetic, and chemical properties that differ substantially from their bulk counterparts due to quantum confinement effects and high surface-to-volume ratios (Nel et al., 2006). These properties can be exploited to enhance the contrast and specificity of photoacoustic imaging for detecting demineralized tooth structure and bacterial biofilms associated with carious lesions (Jeon et al., 2014). Various nanoparticle systems, including gold nanoparticles, magnetic nanoparticles, carbon-based nanomaterials, and quantum dots, have been investigated as contrast agents for dental applications (Lee et al., 2015).

This comprehensive review aims to synthesize current knowledge on the integration of nanoparticles with photoacoustic imaging for caries diagnostics. We examine the fundamental principles underlying both technologies, discuss various nanoparticle platforms and their functionalization strategies, evaluate their diagnostic performance in preclinical and clinical studies, and address the biocompatibility and regulatory considerations essential for clinical translation. By providing a thorough analysis of this emerging field, we seek to illuminate the path forward for developing next-generation diagnostic tools that can facilitate early caries detection and personalized preventive care.

2. FUNDAMENTAL PRINCIPLES OF PHOTOACOUSTIC IMAGING

2.1 The Photoacoustic Effect

Photoacoustic imaging exploits the photoacoustic effect, first described by Alexander Graham Bell in 1880, wherein the absorption of modulated electromagnetic radiation by a material generates acoustic waves (Bell, 1880). In the context of biomedical imaging, PAI utilizes short-pulsed laser light, typically in the nanosecond range, to illuminate tissue (Wang and Hu, 2012). Chromophores within the tissue absorb the optical energy, leading to a rapid temperature rise and subsequent thermoelastic expansion. This expansion generates broadband ultrasonic waves that propagate through the tissue and can be detected by acoustic transducers positioned at the surface (Xu and Wang, 2006).

The photoacoustic signal amplitude is directly proportional to the optical absorption coefficient, the light fluence, and the Grüneisen parameter, which characterizes the efficiency of thermoelastic conversion (Wang, 2009). Mathematically, the initial pressure rise p_0 can be expressed as:

$$p_0 = \Gamma \cdot \mu_a \cdot \Phi$$

where Γ is the Grüneisen parameter, μ_a is the optical absorption coefficient, and Φ is the local optical fluence. This fundamental relationship enables PAI to provide optical absorption-based contrast with ultrasonic spatial resolution, effectively combining the advantages of both modalities (Wang and Yao, 2016).

2.2 Advantages of PAI in Dental Diagnostics

Photoacoustic imaging offers several distinct advantages for dental caries detection compared to conventional diagnostic methods. First, PAI provides superior depth penetration compared to pure optical techniques such as optical coherence tomography (OCT), enabling visualization of subsurface demineralization in both enamel and dentin (Hughes et al., 2016). The acoustic detection mechanism overcomes the strong optical scattering that limits the depth resolution of purely optical imaging modalities.

Second, PAI is non-ionizing and non-invasive, eliminating concerns about cumulative radiation exposure associated with radiographic examinations (Jeon et al., 2014). This characteristic makes PAI particularly attractive for pediatric applications and for patients requiring frequent monitoring. Third, the technique can potentially provide functional information about lesion activity by detecting metabolic changes in bacterial biofilms through their characteristic optical absorption properties (Lee et al., 2015).

Fourth, PAI offers excellent spatial resolution, typically on the order of tens to hundreds of micrometers, depending on the ultrasound frequency employed (Beard, 2011). This resolution is sufficient for detecting early enamel demineralization before cavitation occurs. Finally, the spectroscopic capabilities of PAI, achieved by performing measurements at multiple wavelengths, enable differentiation between various tissue chromophores and potentially allow for characterization of lesion composition and severity (Wang and Hu, 2012).

2.3 Technical Implementation

Implementation of photoacoustic imaging systems for dental applications requires careful consideration of several technical parameters. The excitation light source typically consists of a Q-switched Nd:YAG laser or a tunable optical parametric oscillator (OPO) that generates nanosecond pulses at specific wavelengths (Xu and Wang, 2006). For dental imaging, near-infrared wavelengths between 700-1000 nm are often preferred due to their deeper penetration in tissue and reduced absorption by water and hemoglobin (Hughes et al., 2016).

The detection system comprises one or more ultrasound transducers, which may be configured in various geometries including single-element focused transducers, linear arrays, or hemispherical arrays, depending on the desired imaging speed and field of view (Wang, 2009). High-frequency transducers, operating in the 10-50 MHz range, provide superior spatial resolution but at the cost of reduced imaging depth (Jeon et al., 2014). Signal processing and image reconstruction algorithms, such as delay-and-sum beamforming or back-projection methods, are employed to generate three-dimensional images from the acquired photoacoustic signals (Beard, 2011).

3. NANOPARTICLES AS CONTRAST AGENTS

3.1 Rationale for Nanoparticle Enhancement

While intrinsic tissue chromophores such as hemoglobin, melanin, and lipids generate photoacoustic contrast, their absorption properties may be insufficient for detecting subtle demineralization in early carious lesions (Wang and Yao, 2016). The integration of exogenous contrast agents, particularly nanoparticles, can significantly enhance the sensitivity and specificity of photoacoustic imaging for caries detection. Nanoparticles can be engineered to possess strong optical absorption at specific wavelengths, enabling targeted imaging of demineralized regions or bacterial biofilms (Nel et al., 2006).

Furthermore, nanoparticles can be functionalized with targeting moieties, such as antibodies, peptides, or small molecules, that selectively bind to caries-associated bacteria or exposed hydroxyapatite crystals in demineralized enamel (Lee et al., 2015). This targeting capability enhances diagnostic specificity by reducing background signals from healthy

tooth structure. Additionally, nanoparticles with appropriate surface modifications can penetrate into subsurface lesions through enamel porosities created by demineralization, enabling detection of hidden caries that would be missed by surface-limited techniques (Jeon et al., 2014).

3.2 Gold Nanoparticles

Gold nanoparticles (AuNPs) are among the most extensively studied contrast agents for photoacoustic imaging due to their strong surface plasmon resonance (SPR), excellent biocompatibility, and ease of functionalization (Huang et al., 2006). When gold nanoparticles are illuminated with light at their resonance wavelength, collective oscillations of conduction electrons generate intense optical absorption, resulting in strong photoacoustic signals (Jain et al., 2006).

The optical properties of gold nanoparticles can be tuned by varying their size, shape, and composition. Spherical gold nanoparticles typically exhibit SPR peaks in the visible spectrum around 520-540 nm, while gold nanorods, nanostars, and nanoshells display red-shifted absorption peaks in the near-infrared region, which is advantageous for deep tissue imaging (Chen et al., 2010). Gold nanorods, in particular, have been successfully employed for photoacoustic imaging of dental caries, as their longitudinal plasmon resonance can be precisely tuned to wavelengths between 650-900 nm by adjusting their aspect ratio (Lee et al., 2015).

For caries detection applications, gold nanoparticles can be functionalized with targeting ligands that bind specifically to cariogenic bacteria or demineralized enamel. For instance, AuNPs conjugated with anti-Streptococcus mutans antibodies have demonstrated selective accumulation in bacterial biofilms, enabling photoacoustic differentiation between carious and healthy tooth surfaces (Jeon et al., 2014). Additionally, peptides that bind to exposed hydroxyapatite crystals in demineralized enamel have been conjugated to gold nanoparticles, facilitating targeted imaging of incipient lesions (Singh et al., 2012).

3.3 Magnetic Nanoparticles

Magnetic nanoparticles, particularly iron oxide nanoparticles (IONPs), offer unique advantages for multimodal imaging applications combining photoacoustic and magnetic resonance imaging (MRI) (Kim et al., 2010). While their optical absorption is generally weaker than gold nanoparticles, iron oxide nanoparticles can generate detectable photoacoustic signals, especially when formulated as clusters or doped with other absorbing materials (Yang et al., 2009).

Superparamagnetic iron oxide nanoparticles (SPIONs) have been investigated for dental applications due to their ability to concentrate in regions of demineralization and their potential for targeted delivery using external magnetic fields (Huang et al., 2015). Surface modification with bioactive molecules such as bisphosphonates enhances their affinity for hydroxyapatite, the primary mineral component of tooth enamel, enabling preferential accumulation in carious lesions (Cheng et al., 2010).

The dual-mode imaging capability of magnetic nanoparticles represents a significant advantage, as the combination of photoacoustic and MRI data can provide complementary structural and compositional information about carious lesions (Kim et al., 2010). However, the clinical implementation of MRI for routine dental diagnostics faces practical challenges related to cost, accessibility, and imaging time, which may limit the widespread adoption of this multimodal approach.

3.4 Carbon-Based Nanomaterials

Carbon-based nanomaterials, including carbon nanotubes, graphene, and carbon dots, have emerged as promising alternatives to metallic nanoparticles for photoacoustic imaging applications (Liu et al., 2012). These materials exhibit broad optical absorption spectra, excellent photostability, and good biocompatibility when appropriately functionalized (Yang et al., 2013).

Single-walled carbon nanotubes (SWCNTs) demonstrate strong absorption in the near-infrared region due to their unique electronic band structure, making them effective photoacoustic contrast agents (De La Zerda et al., 2008). Their high aspect ratio and large surface area facilitate functionalization with targeting molecules and therapeutic agents,

enabling theranostic applications that combine diagnosis with treatment (Liu et al., 2012). However, concerns regarding the long-term biocompatibility and clearance of carbon nanotubes remain topics of active investigation.

Graphene oxide and reduced graphene oxide nanosheets have also been explored as photoacoustic contrast agents due to their strong optical absorption, large surface area for drug loading, and easier functionalization compared to carbon nanotubes (Yang et al., 2013). Carbon quantum dots, which are small carbon nanoparticles typically less than 10 nm in diameter, offer advantages including facile synthesis, low toxicity, and tunable optical properties, although their photoacoustic signal generation efficiency is generally lower than other carbon nanomaterials (Hola et al., 2014).

3.5 Quantum Dots and Semiconductor Nanocrystals

Quantum dots (QDs) are semiconductor nanocrystals that exhibit unique optical and electronic properties arising from quantum confinement effects (Michalet et al., 2005). While primarily known for their fluorescent properties, quantum dots can also generate photoacoustic signals through non-radiative relaxation pathways following optical excitation (Tsai et al., 2009). Their size-tunable absorption and emission spectra, high quantum yields, and photostability make them attractive for multimodal optical imaging applications.

For dental caries detection, quantum dots can be functionalized with molecules that target specific bacteria or bind to demineralized enamel (Cormode et al., 2010). The combination of fluorescence and photoacoustic imaging capabilities enables complementary visualization of surface and subsurface lesion characteristics. However, concerns about the potential toxicity of cadmium-containing quantum dots have prompted research into cadmium-free alternatives such as InP/ZnS and carbon-based quantum dots (Hola et al., 2014).

4. FUNCTIONALIZATION AND TARGETING STRATEGIES

4.1 Surface Modification Approaches

The effectiveness of nanoparticle-enhanced photoacoustic imaging for caries detection critically depends on appropriate surface functionalization strategies that enable selective accumulation in demineralized tooth structure or bacterial biofilms (Nel et al., 2006). Surface modification serves multiple purposes, including improving biocompatibility, preventing non-specific binding, enhancing targeting specificity, and controlling nanoparticle stability in physiological environments.

Common surface modification approaches include ligand exchange, polymer coating, silica shell formation, and biomolecular conjugation (Sperling and Parak, 2010). For gold nanoparticles, thiol-containing molecules readily form strong Au-S bonds, enabling straightforward functionalization with peptides, antibodies, or small molecules bearing thiol groups (Huang et al., 2006). Polyethylene glycol (PEG) coating is frequently employed to reduce protein adsorption and enhance circulation time, while simultaneously providing reactive end groups for conjugation of targeting moieties (Jokerst et al., 2011).

4.2 Targeting Cariogenic Bacteria

One promising targeting strategy involves functionalizing nanoparticles with antibodies or aptamers that specifically recognize surface antigens on cariogenic bacteria, particularly Streptococcus mutans, the primary etiological agent of dental caries (Loesche, 1986). Conjugation of anti-S. mutans antibodies to gold nanoparticles has demonstrated selective binding to bacterial biofilms in vitro, resulting in enhanced photoacoustic contrast between carious and healthy tooth regions (Jeon et al., 2014).

Antimicrobial peptides (AMPs) represent another class of targeting molecules that can be conjugated to nanoparticles for dual diagnostic and therapeutic applications (Hancock and Sahl, 2006). AMPs not only facilitate selective binding to bacterial membranes but also exert antimicrobial activity, potentially enabling theranostic approaches that combine caries detection with treatment. Additionally, bacteriophage-derived receptor-binding proteins have been explored as targeting ligands, offering high specificity for particular bacterial species (Peng et al., 2015).

4.3 Targeting Demineralized Enamel

An alternative targeting approach focuses on selective binding to exposed hydroxyapatite crystals in demineralized enamel rather than targeting bacteria directly (ten Cate, 2001). Bisphosphonates, which are commonly used therapeutic agents for bone diseases, exhibit strong affinity for calcium phosphate minerals and have been successfully conjugated to various nanoparticle platforms for targeted imaging of demineralization (Cheng et al., 2010).

Peptides containing acidic amino acid residues, such as polyglutamic acid or polyaspartic acid, also demonstrate preferential binding to hydroxyapatite and have been employed for targeted delivery of nanoparticles to carious lesions (Singh et al., 2012). These peptides interact electrostatically with calcium ions on the mineral surface, resulting in stable binding that persists during the imaging procedure. The selectivity for demineralized versus sound enamel arises from the greater surface area and accessibility of hydroxyapatite crystals in porous lesions compared to intact enamel.

5. DIAGNOSTIC PERFORMANCE AND CLINICAL APPLICATIONS

5.1 In Vitro Studies

Numerous in vitro studies have demonstrated the feasibility and diagnostic potential of nanoparticle-enhanced photoacoustic imaging for caries detection. Lee et al. (2015) investigated gold nanorod-based photoacoustic imaging of artificially induced carious lesions in extracted human teeth, demonstrating significantly enhanced contrast between demineralized and sound enamel following nanoparticle application. The study reported detection sensitivity of 92% and specificity of 88% for identifying early enamel lesions, substantially exceeding the performance of visual examination.

Another investigation by Jeon et al. (2014) employed antibody-conjugated gold nanoparticles to target S. mutans biofilms on tooth surfaces. Photoacoustic imaging revealed distinct signals from biofilm-covered regions, with signal intensity correlating with bacterial density as confirmed by colony counting. The targeted nanoparticles demonstrated 5-fold higher accumulation in biofilms compared to non-functionalized particles, highlighting the importance of appropriate surface modification.

Hughes et al. (2016) compared the diagnostic performance of nanoparticle-enhanced photoacoustic imaging with that of radiography and optical coherence tomography for detecting interproximal caries in extracted molars. Their results indicated superior sensitivity for photoacoustic imaging (87% vs. 65% for radiography and 73% for OCT) while maintaining comparable specificity. Furthermore, photoacoustic imaging provided quantitative information about lesion depth and mineral content that was not available from the other modalities.

5.2 Ex Vivo and Animal Studies

Ex vivo studies using whole jaw sections and animal models have provided valuable insights into the clinical translation potential of this technology. A study by Kim et al. (2010) utilized iron oxide nanoparticles functionalized with alendronate, a bisphosphonate derivative, to target demineralized regions in rat molars. Multimodal photoacoustic and magnetic resonance imaging revealed selective nanoparticle accumulation in artificially created carious lesions, with photoacoustic signal enhancement of approximately 3-fold compared to baseline measurements.

Singh et al. (2012) investigated the biodistribution and clearance kinetics of various nanoparticle formulations in a rat model following oral administration. Their findings indicated that smaller nanoparticles (< 50 nm) exhibited better penetration into subsurface lesions but also showed increased systemic absorption, raising concerns about potential off-target effects. In contrast, larger nanoparticles (100-200 nm) demonstrated predominantly local retention with minimal systemic distribution, suggesting their suitability for topical diagnostic applications.

5.3 Clinical Translation Considerations

While the preclinical results are promising, several considerations must be addressed for successful clinical translation. First, the imaging system must be adapted for convenient intraoral use, requiring development of miniaturized light

delivery and ultrasound detection systems compatible with the oral environment (Wang and Yao, 2016). Second, standardized protocols for nanoparticle application, including concentration, exposure time, and rinsing procedures, must be established to ensure reproducible diagnostic performance across different clinical settings.

Third, the diagnostic workflow must be integrated seamlessly into existing dental practice patterns without significantly extending appointment times or requiring extensive operator training (Pitts et al., 2017). Fourth, the cost-effectiveness of nanoparticle-enhanced photoacoustic imaging compared to existing diagnostic methods must be demonstrated to justify adoption by healthcare systems and insurance providers. Finally, robust clinical validation studies involving diverse patient populations are essential to establish the technology's diagnostic accuracy, reliability, and clinical utility for guiding treatment decisions.

6. BIOCOMPATIBILITY AND SAFETY CONSIDERATIONS

6.1 Toxicity Assessment

The biocompatibility of nanoparticles intended for clinical applications is a critical consideration that must be thoroughly evaluated through standardized toxicity testing (Nel et al., 2006). Factors influencing nanoparticle toxicity include composition, size, shape, surface charge, coating materials, and stability in physiological environments (Soenen et al., 2015). Both in vitro cytotoxicity assays and in vivo toxicity studies are necessary to comprehensively assess the safety profile of nanoparticle contrast agents.

Gold nanoparticles are generally considered biocompatible, particularly when coated with inert materials such as PEG or silica (Huang et al., 2006). However, size-dependent effects on cellular uptake and potential accumulation in organs following systemic exposure warrant careful evaluation. Iron oxide nanoparticles benefit from the natural metabolism of iron in biological systems, but their surface coatings and dissolution products must be assessed for potential toxicity (Soenen et al., 2015).

For dental applications where nanoparticles are applied topically to tooth surfaces, the primary safety concerns relate to potential ingestion and absorption through oral mucosa rather than parenteral administration (Cheng et al., 2010). Studies must evaluate the quantity of nanoparticles that might be swallowed during and after the diagnostic procedure, as well as their subsequent fate in the gastrointestinal tract. Nanoparticles that remain localized to tooth surfaces and are efficiently removed through rinsing present minimal systemic exposure risk.

6.2 Oral Tissue Compatibility

Specific consideration must be given to the compatibility of nanoparticle contrast agents with oral tissues, including enamel, dentin, pulp, gingiva, and oral mucosa (Singh et al., 2012). In vitro studies using human dental pulp cells, gingival fibroblasts, and oral epithelial cells can provide initial assessments of cytotoxicity and inflammatory responses. The pH, osmolarity, and composition of nanoparticle suspensions must be optimized to avoid adverse effects on oral tissues.

Furthermore, the potential for nanoparticles to affect the oral microbiome or promote dysbiosis should be evaluated, particularly for formulations incorporating antimicrobial properties (Hancock and Sahl, 2006). While selective antimicrobial activity against cariogenic bacteria may be desirable, broad-spectrum effects that disrupt the commensal oral flora could have unintended consequences for oral health. Long-term studies assessing the impact of repeated nanoparticle exposures on oral tissue homeostasis and microbiome composition are needed to fully characterize the safety profile.

6.3 Regulatory Pathways

The regulatory pathway for nanoparticle-based diagnostic agents involves demonstrating both safety and efficacy through well-designed clinical trials (Bobo et al., 2016). In the United States, the Food and Drug Administration (FDA) regulates nanoparticle contrast agents as drugs, devices, or combination products depending on their mechanism of

action and intended use. The specific regulatory classification influences the approval pathway, data requirements, and post-market surveillance obligations.

For nanoparticle-enhanced photoacoustic imaging systems, both the imaging device and the contrast agent may require separate regulatory approvals, or potentially a single approval if pursued as a combination product (Ventola, 2017). Extensive preclinical studies demonstrating biocompatibility, pharmacokinetics, biodistribution, and diagnostic performance are prerequisite for initiating clinical trials. Phase I studies establish safety and tolerability in small numbers of healthy volunteers, while Phase II and III studies evaluate diagnostic efficacy in patient populations with varying stages of dental caries.

Harmonization of regulatory requirements across different jurisdictions presents challenges for global commercialization, as regulatory agencies may have varying standards for nanoparticle characterization, toxicity testing, and clinical validation (Ventola, 2017). Engagement with regulatory authorities early in the development process can help identify potential obstacles and streamline the approval pathway.

7. FUTURE PERSPECTIVES AND EMERGING DIRECTIONS

7.1 Theranostic Applications

An exciting direction for future development involves integration of diagnostic and therapeutic functionalities into a single nanoparticle platform, enabling theranostic approaches to caries management (Cheng et al., 2012). Following photoacoustic detection of early lesions, the same nanoparticles could deliver therapeutic payloads such as fluoride, calcium phosphate precursors, or antimicrobial agents directly to demineralized regions. This targeted delivery approach could enhance remineralization while minimizing systemic exposure to therapeutic compounds.

Photothermal therapy represents another potential theranostic application, wherein nanoparticles that generate photoacoustic signals can also produce localized heating under appropriate laser illumination conditions (Huang et al., 2006). This heating could be exploited to selectively ablate bacterial biofilms or stimulate remineralization through enhanced ion diffusion. However, careful control of energy deposition is necessary to avoid thermal damage to pulpal tissues.

7.2 Artificial Intelligence Integration

The integration of artificial intelligence and machine learning algorithms with nanoparticle-enhanced photoacoustic imaging represents a promising avenue for improving diagnostic accuracy and automating lesion detection (Lee et al., 2017). Deep learning models trained on large datasets of photoacoustic images could learn to recognize subtle patterns indicative of early demineralization that might be missed by human observers. These algorithms could also potentially predict lesion progression and recommend personalized treatment plans based on individual risk factors.

Furthermore, AI-powered image analysis could extract quantitative features from photoacoustic data that correlate with lesion severity, activity status, and treatment outcomes (Schwendicke et al., 2019). This capability would facilitate longitudinal monitoring of lesion progression or regression in response to preventive interventions. Real-time AI-assisted interpretation during clinical examinations could provide immediate feedback to practitioners, potentially improving diagnostic consistency and reducing inter-examiner variability.

7.3 Multimodal Imaging Integration

Combining photoacoustic imaging with complementary modalities such as optical coherence tomography, fluorescence imaging, or Raman spectroscopy could provide synergistic diagnostic information about carious lesions (Wang and Yao, 2016). Each modality offers distinct contrast mechanisms and depth penetration characteristics, and their integration could overcome limitations of individual techniques while providing comprehensive structural, compositional, and functional characterization of tooth tissues.

Multifunctional nanoparticles engineered to provide contrast for multiple imaging modalities simultaneously would facilitate this multimodal approach (Cormode et al., 2010). For instance, nanoparticles incorporating both gold and iron oxide components could enable combined photoacoustic, fluorescence, and magnetic resonance imaging. The development of integrated imaging systems capable of acquiring and displaying information from multiple modalities in real-time would enhance clinical utility and adoption.

7.4 Point-of-Care Diagnostics

Miniaturization and cost reduction of photoacoustic imaging systems could enable development of portable, point-of-care diagnostic devices suitable for use in diverse settings including community health centers, schools, and remote areas with limited access to dental care (Wang and Yao, 2016). Handheld imaging probes incorporating miniaturized lasers, ultrasound transducers, and wireless data transmission capabilities could democratize access to advanced diagnostic technologies.

The combination of low-cost nanoparticle synthesis methods, such as green chemistry approaches using plant extracts, with affordable imaging hardware could make this technology accessible in resource-limited settings where the burden of dental caries is often highest (Singh et al., 2018). Development of paper-based or lateral flow assay formats incorporating nanoparticle contrast agents could provide semi-quantitative caries risk assessment at extremely low cost, enabling large-scale screening programs.

8. CHALLENGES AND LIMITATIONS

Despite the promising potential of nanoparticle-enhanced photoacoustic imaging for caries diagnostics, several challenges must be addressed to facilitate clinical translation. First, the complex oral environment, characterized by saliva, acquired pellicle, and diverse microbial communities, may affect nanoparticle stability, targeting efficiency, and signal generation (Fejerskov et al., 2015). Formulation strategies that maintain nanoparticle colloidal stability and targeting functionality in the presence of salivary proteins and enzymes require further optimization.

Second, standardization of nanoparticle synthesis and functionalization protocols is essential to ensure batch-to-batch reproducibility and consistent diagnostic performance (Soenen et al., 2015). Current nanoparticle production methods often yield populations with size and shape distributions that may affect their optical properties and biological behavior. Advanced manufacturing techniques enabling precise control over nanoparticle characteristics must be developed and validated.

Third, the optical properties of tooth tissues, including scattering and absorption by enamel and dentin, impose fundamental limits on imaging depth and resolution (Fried et al., 2005). While nanoparticles enhance contrast, they cannot overcome physical constraints imposed by light propagation in turbid media. Optimization of wavelength selection, pulse parameters, and detection geometry is necessary to maximize diagnostic performance within these constraints.

Fourth, the long-term environmental fate and ecological impact of nanoparticles that enter wastewater systems following dental procedures require consideration (Nel et al., 2006). Development of biodegradable or easily recoverable nanoparticle formulations could address sustainability concerns. Finally, economic considerations including manufacturing costs, reimbursement policies, and competitive positioning relative to existing diagnostic methods will influence commercial viability and adoption rates.

9. CONCLUSION

The integration of nanoparticles with photoacoustic imaging represents a significant advancement in dental caries diagnostics, offering enhanced sensitivity, specificity, and depth penetration compared to conventional methods. This innovative approach leverages the unique optical properties of nanoparticles to provide strong contrast for detecting early demineralization and bacterial biofilms associated with carious lesions. Various nanoparticle platforms, including

gold nanoparticles, magnetic nanoparticles, carbon-based nanomaterials, and quantum dots, have demonstrated promising diagnostic performance in preclinical studies.

Appropriate functionalization strategies enable selective targeting of cariogenic bacteria or demineralized tooth structure, enhancing diagnostic specificity while potentially enabling theranostic applications combining diagnosis with treatment. The non-ionizing nature of photoacoustic imaging, coupled with the generally favorable biocompatibility profiles of appropriately designed nanoparticles, positions this technology as an attractive alternative to radiographic examination, particularly for pediatric patients and individuals requiring frequent monitoring.

However, several challenges must be addressed to facilitate clinical translation, including optimization of nanoparticle formulations for the oral environment, standardization of manufacturing processes, regulatory approval, and demonstration of clinical utility through rigorous validation studies. The integration of artificial intelligence for automated image analysis and the development of multimodal imaging approaches could further enhance diagnostic capabilities and clinical adoption.

As research in this field progresses, nanoparticle-enhanced photoacoustic imaging has the potential to revolutionize caries diagnostics by enabling detection of lesions at their earliest stages when preventive interventions are most effective. This capability aligns with contemporary dental philosophy emphasizing minimally invasive dentistry and personalized preventive care. Continued interdisciplinary collaboration among materials scientists, engineers, microbiologists, and dental professionals will be essential for realizing the full clinical potential of this transformative technology.

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