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NANOTECHNOLOGY-BASED DENTAL THERAPEUTICS AND THEIR RENAL SAFETY IMPLICATIONS

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ABSTRACT
Nanotechnology-based dental therapeutics have gained widespread clinical adoption due to enhanced antimicrobial activity, improved mechanical performance, and the ability to enable targeted drug delivery within oral tissues. Despite these advantages, accumulating evidence indicates that nanoscale dental materials may access systemic circulation through oral mucosal absorption, ingestion, procedural vascular entry, and chronic low-dose release from restorative interfaces, raising concerns regarding renal biodistribution and nephrotoxicity. This review synthesizes current experimental, preclinical, and translational evidence addressing systemic exposure routes, renal handling mechanisms, and kidney-related safety risks associated with dental nanotherapeutics. A comprehensive narrative evaluation was undertaken focusing on physicochemical determinants of nanoparticle behavior, including size, surface charge, composition, and protein corona formation, which collectively influence renal filtration, tubular uptake, and clearance. Findings from in vitro renal cell models and animal studies consistently identify oxidative stress, inflammatory activation, mitochondrial dysfunction, and tubular injury as central mechanisms underlying nanoparticle-induced renal toxicity. Evidence further suggests that renal accumulation and functional impairment are dose- and exposure-duration-dependent, with heightened vulnerability observed in patients with chronic kidney disease and renal transplant recipients. Limited long-term human clinical data underscore the need for cautious translational interpretation and targeted safety evaluation. Integrating nephrology-focused risk assessment into dental nanomedicine development, alongside interdisciplinary collaboration and nephroprotective material design, is therefore essential to support responsible clinical translation and safeguard kidney health.

KEYWORDS: Dental nanotechnology; Renal safety; Nanoparticle biodistribution; Nephrotoxicity; Risk assessment

1. INTRODUCTION
Modern dental therapeutics is still being transformed by nanotechnology in the form of nanoscale materials and vaccines designed to perform better in antimicrobial effects, mechanical functionality, and specifically in bioactivity in oral tissues [1]. Nanoparticles have been shown to have clinical interests that are growing fast due to the capacity to strengthen restorative matrices, prevent the formation of biofilms, and deliver drugs locally in periodontal and implant therapy [2]. Further studies on dental implant nano-engineering have proved that the surface-modified nano structures enhance the functions of nano-engineering namely surface nano structures in regard to their capacity to promote the process of osseointegration and antimicrobial resistance which are of clinical importance in modern dental delivery [3]. Simultaneous advances in nanomaterial engineering have placed even greater emphasis on the physicochemical characterization of nanomaterials. Such parameters as composition, surface chemistry, wettability, and thermal stability play a critique role in determining the behavior of nanoparticles in biological systems [4]. Such qualities control aggregation, dissolution and interaction with bio-fluids thus defining therapeutic performance and systemic safety expectations [5]. Such characterization in the context of dentistry forms the basis of rational design of nano-enabled composites and coating as well as the frameworks of anticipatory safety assessment [6].
Systemic exposure is also more likely to occur due to an increase in clinical use of dental nanotherapeutics. It has been experimentally shown that nanoparticles are released by dental composites and restorative materials during mechanical wear and aging conditions [7]. Contact with mucous membranes of the mouth, unintended intake, disruption of the tissues

during the procedure, and the inability to prevent a low dose of nanoparticles with repeated dental care throughout life are all contributors to nanoparticles entering the systemic circulation [8]. According to the toxicological literature, engineered nanomaterials have a different biological behavior to bulk materials and require organs-specific risk assessment [9]. The kidney is one of the systemic target organs that deserve specific attention as it has a high perfusion rate and filtration and tubular transportation are highly specific. Factors that determine nanoparticle biodistribution and clearing are size, surface charge and reaction with biological components, any of which can alter renal exposure profiles [10]. Nanomedicine has demonstrated evidence that it is possible to selectively target renal tubules and glomerular compartments, which ensure that nanoparticles can be localized to kidney structures under physicochemical conditions [11].

The renal clearance mechanisms also make the issue of safety complicated. In experimental research, it is shown that nanomaterials smaller than 10nm can be efficiently eliminated by the kidney but slight increments in hydrodynamic size led to renal retention and tissue engagement [12]. Further evidence shows that the geometry of nanoparticles and their lateral dimension influence whether a renal processing occurs via glomerular filtration or alternative processes [13]. Mechanistic studies also implicate such parameters with selective kidney damage in certain classes of nanomaterials [14]. The argument of assessing renal safety and nephrotoxicity of dental nanotherapeutics thus goes beyond mere consideration. The toxicity of nanoparticles is always associated with oxidative stress and inflammatory activation as the key pathways of injury in the renal tissue [15]. Nanoparticles based on metals that have been used as antimicrobial agents in dentistry have redox characteristics and ion-release properties that can potentially enhance renal susceptibility when taken systemically [8]. Individual studies of zinc oxide nanoparticles reveal that oxidative and inflammatory pathways involved in kidney damage have been modulated, which further supports the importance of endpoints in kidney damage in nanomaterial toxicology studies [16].

Translational safety assessment is also paying increased attention to organized risk-minimization approaches specific to nanomedicine. Safe-by-design methods combine the physicochemical optimization to predictive toxicology to reduce the adverse effects before they become clinical disseminated [17]. Regulatory reviews also underscore the challenge of assessing products containing nanomaterials and especially where the traditional bioequivalence and toxicity paradigms are not adequate [18]. These issues are consistent with more general arguments about clinical translation of nanomedicines [19]. Applicability to nephrology is specifically strong in relation to patients having chronic kidney disease, which have reduced clearance ability and are sensitive to nephrotoxic stressors. Renal nanomedicine has shown that low doses in the systemic state can be clinically relevant in diseased kidney dysfunction [20]. In line with this, this review situates dental nanotherapeutics within a nephrology-oriented context, requiring innovation in oral health to be connected to pathways of kidney exposure, determinants of renal handling and mechanisms of nephrotoxicity and their associated implications of evidence-based risk assessment [10]. This review aims to summarize systemic exposure pathways of dental nanotherapeutics and their renal biodistribution, to examine mechanisms of nanoparticle-induced renal toxicity and to evaluate renal safety implications of dental nanotherapeutics in clinical practice

2. Overview of Nanotechnology-Based Dental Therapeutics

The application of nanotechnology in contemporary dental therapeutics has transformed modern-day dental practice by incorporating the use of nanoscale materials with an improved physicochemical, biological, and functional property. This is the surface area is enhanced through a reduction of the material dimensions to the nanometre range which enhances the reactivity, bioavailability, and interaction with the biological tissue. These properties promote excellent antimicrobial action, remineralization ability, mechanical power, and regulated drug discharge. Dental nanotherapeutics are thus a clinical pertinent group of materials that has both local therapeutic effect as well as systemic exposure such as renal safety.

2.1 Types of Nanomaterials Used in Dentistry

2.1.1 Metallic Nanoparticles

One of the most widely studied categories of nanomaterials in dental practice is represented by the metallic nanoparticles with their high antimicrobial and antibiofilm properties [21]. Silver, gold, zinc oxide, titanium dioxide and copper nanoparticles have bactericidal effects by direct contact with microbial cell membranes, oxidative stress, and metabolism [21]. These properties have enabled them to be incorporated into restorative composites, adhesives, endodontic sealers and implant surfaces to prevent the development of secondary caries and peri-implant infections [22]. Nevertheless, the surface reactivity and persistence of metallic nanoparticles are high, and this raises the issues of systemic dissemination and renal retention, which fosters the necessity of safety-oriented material design [23].

2.1.2 Polymeric Nanoparticles

Biodegradable and biocompatible are also used to form polymeric nanoparticles, including chitosan, poly(lactic-coglycolic acid), polyethylene glycol, and alginate, which has a better safety profile, compared to inorganic nanomaterials [24]. These systems allow controlled release of drugs, increased cohesion and stability of therapeutic agents. Polymeric nanoparticles can act as carriers of antimicrobials, anti-inflammatory agents and regenerative molecules in dental therapeutics to facilitate localized treatment approaches [21]. The fact that they can be optimized in terms of tenable size, surface charge and degradation kinetics to be used in dental applications, without neglecting systemic absorption with regard to renal transport and clearance processes, is important [25].

2.1.3 Nano-Hydroxyapatite

The mineral form of natural enamel and dentin is very similar to nano-hydroxyapatite, which is why it is especially applicable in the remineralization and regenerative dental treatment [21]. The structure of this nanoscale increases surface reactivity and bio integration, thereby favouring repair of enamel, reduction of dentin hypersensitivity and bone regeneration. Nano-hydroxyapatite is popularly used in toothpastes, dental varnishes, restorative material and graft substitutes. Although it has a good biocompatibility, long-term exposure and possible aggregation bring to the fore issues associated with the renal filtration rate and long-term safety [25].

2.1.4. Lipid-Based Nanocarrier. 2.1.4.2 Hybrid Nanocarrier.

The lipid-based nanocarriers such as liposomes, solid lipid nanoparticles and nanostructured lipid carriers have high capacity of drug-loading and effective penetration into tissues of the mouth [24]. Antimicrobial efficacy and sustained release properties Multifunctionality is accomplished in hybrid nanocarriers, formed by the incorporation of antimicrobial activity with lipids, polymeric or inorganic building blocks. These systems are finding use in periodontal therapy, surface modification of implants as well as in local drug delivery applications [22]. Their biodegradability character usually favours renal excretion; surface functionalization and composite structure could modify biodistribution and renal excretion [25].

2.2 Therapeutic Applications in Dentistry

2.2.1 Restorative Materials

Restorative materials modified by nanotechnology have high mechanical strength, wearability, aesthetics and antimicrobial characteristics than conventional formulations [21]. The nanofillers minimize polymerization contraction and enhance the surface finish, whereas embedded nanoparticles prevent bacteria growth at restoration boundaries [23].

2.2.2 Endodontic Disinfection

Nanoparticles enhance the disinfection of root canals by entering dentinal tubules and achieving long-term antimicrobial effect on periodontal pathogens and biofilms that are resistant to metronidazole. Metallic and polymeric nanoparticle both prove to be more effective compared to conventional irrigants and medicaments [22].

2.2.3 Periodontal Therapy

Systems based on nanocarriers allow the selection of local delivery of antimicrobials, anti-inflammatory agents and regenerative compounds in periodontal pockets. This topical treatment is more effective in enhancing the treatment response and reducing the systemic exposure of drugs [24].

2.2.4 Implant Coatings and Drug Delivery.

Dental implants that are coated with nanoparticles improve the process of integration with the bone, minimise the adhesion of microorganisms, and favour the localised forms of drug administration illustrated in Table 1. Those properties provide long-term stability of implants and a decrease in peri-implant disease [21].

Table 1. Classification of Dental Nanotherapeutics, Composition, Size Range, and Clinical Application

Nanomaterial Type	Typical Composition	Approximate Size Range (nm)	Principal Dental Applications	Key Reference
Metallic nanoparticles	Silver, gold, zinc oxide, titanium dioxide	5–100	Restorative composites, antimicrobial coatings, endodontic sealers, implant surfaces	[21]
Polymeric nanoparticles	Chitosan, PLGA, PEG, alginate	50–300	Drug delivery systems, periodontal therapy, endodontic disinfection	[24]
Nanohydroxyapatite	Calcium phosphate–based apatite	20–80	Enamel remineralization, dentin hypersensitivity management, bone regeneration	[21]
Lipid-based nanocarriers	Liposomes, solid lipid nanoparticles	50–200	Periodontal drug delivery, mucosal penetration, antiinflammatory therapy	[22]
Hybrid nanocarriers	Polymer–lipid or inorganic–polymer composites	50–300	Implant coatings, multifunctional drug delivery, sustained antimicrobial action	[25]

3. Dental Nanotherapeutics Pathways of Systemic Exposure.

The most common use of dental nanotherapeutics is in localized therapy in the oral cavity; several exposure pathways allow the translocation of nanoparticles into the bloodstream. High vascularization, repetitive mechanical stress, and

prolonged contact between materials and tissues are some of the characteristics of the oral environment, which contribute to the migration of nanoparticles outside of the target site of action. In the nephrology viewpoint, it is vital to identify these routes of exposure, as it is clearance dynamics that define renal biodistribution and whether toxicity is possible nephrotoxicity [26].

3.1 Oral Mucosal Absorption

The oral mucosa is a semi-permeable and highly vascularized barrier that has the capacity to allow nanoscale materials to be absorbed. Nanoparticles deposited on gingivitis, periodontal pockets or oral mucosa can enter the epithelial layers by paracellular diffusion, transcytosis, or endocytosis. The efficiency of the penetration is highly dependent on the particle size, surface charge and hydrophobicity. Lipid-based and polymeric nanocarriers exhibit better mucosal permeability, and they enhance their therapeutic delivery in addition to enhancing the probability of systemic penetration and downstream exposures to renal pathways [27].

3.2 Ingestion and Gastrointestinal Uptake.

Dental nanomaterials are unintentionally consumed as part of the normal clinical practice and daily consumption of nanoenabled dental care products, such as toothpastes, varnishes, and mouth rinses. After the ingestion, nanoparticles are exposed to the gut mucosa, in which case absorption can take place via enterocytes, Peyer cells or microfold cells. This absorption leads to the entry of nanoparticles into portal and systemic circulation in which they are exposed to the hepatic processing and renal filtration. Persistent consumption, even at low dose, adds to cumulative systemic nanoparticle load with consequences of the renal processing and clearance [28].

3.3 Incidental Systemic Releases in Procedures.

Direct entry into the bloodstream with invasive dental treatments, including periodontal surgery, implant placement, and endodontic surgery, can be used to facilitate nanoparticle entry. Breakage of epithelial and vascular barriers enhances the likelihood of transient release to the systemic circulation especially with nanoparticle-containing irrigant, sealers or implant coating. Even though chronic in nature, such exposure events have the potential to cause acute rises in circulating nanoparticle concentrations, which augment renal filtration load and augment the risk of tubular or glomerular contact [29].

3.4 Reduced dose exposures in the chronic period: Dental materials.

The chronic release of nanoparticles in low doses in terms of restorative composite, sealants, and implant coating is a long-term retention of nanomaterials. With time, mechanical abrasion, chemical and enzymatic activity in the oral environment releases nanoparticles. Repeated exposure to Figure 1 below clinically significant concentrations is a matter of concern when it comes to cumulative renal build up especially in patients with limited clearance capability or existing kidney illness. Regarding the renal safety, chronic exposures critical situations should be considered in the design of nanomaterials and their clinical use [30].

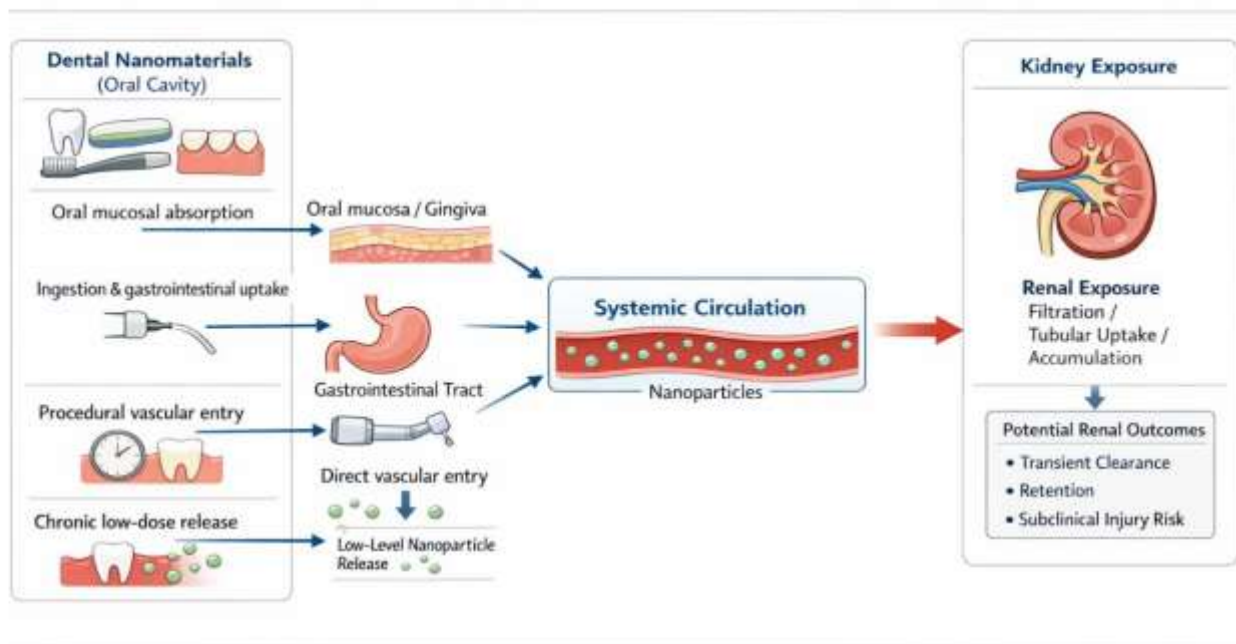

Figure 1. Routes of Systemic Exposure Following Dental Application of Nanomaterials

Illustrative schematic depicting oral mucosal absorption, gastrointestinal uptake following ingestion, procedural vascular entry, and chronic release from dental materials leading to systemic circulation and renal exposure.

4. Biodistribution and Renal Process of Nanoparticles.

After dental nanotherapeutic is released into systemic circulation, the biological fate of the biomolecule is determined by the interactions with blood components and by the renal clearance systems. Kidney is one of the major organs that the nanoparticle can be handled because of high perfusion, filtration structure and tubular epithelium that is metabolically active. In Table 2, the nanoparticle physicochemical properties of biodistribution and renal processing influence the persistence of the circulation, tissue deposition, and nephrotoxicity [25].

4.1 The Circulation, Protein Corona Formation, and

4.1.1 Interaction with Plasma Proteins

After systemic entry, nanoparticles quickly adsorb plasma proteins onto their surface which creates a dynamic protein corona which determines biological identity but not material composition. Corona composition is often largely dominated by albumin, immunoglobulins, fibrinogen and complement proteins, which cause changes in nanoparticle size, surface charge, and immune recognition. The formation of protein corona affects the stability, cellular interaction, and renal filtration behavior of metallic and highly reactive nanomaterials which are used in dental applications [28].

4.1.2 Effect of Intrarenal Filtration.

Nanoparticles with protein coating have different glomerular filtration barrier associations than pristine counterparts do. Heightened hydrodynamic diameter caused by corona formation can reduce the ability of passage through the glomerular basement membrane and some protein-nanoparticle complexes facilitate retention in renal microvasculature. Such transport dynamics cause nanoparticles to be filtered efficiently, retarded, or accumulated progressively in the kidney [25].

4.2 Renal Clearance Mechanisms

4.2.1 Glomerular Filtration

The major clearance route of nanoparticles with sizes that are below critical size ranges is through glomerular filtration. In Figure 2, nanoparticles that have hydrodynamic diameters that are usually less than 5-8 nm exhibited efficient filtration microscopic process into the urinary space, especially in those cases of neutral or mildly anionic surface charges. Nanoparticles that are larger than this size undergo constrained filtration and hence, prolonged systemic circulation and duration of renal exposure [30].

4.2.2 Tubular Incorporation and Retention.

Nanoparticles that go outside or partially cross the glomerular barrier can influence renal tubular epithelial cells directly. The endocytic uptake is mostly found in proximal tubules whereby the reabsorption processes internalize the filtered particles. Metallic and positively charged nanoparticles exhibit superior tubular retention which facilitates intracellular retention, oxidative stress and inflammatory signalling. Constant tubular uptake is an additional cause of subclinical renal thalassemia and an accruing risk of nephrotoxicity [29].

4.2.3 Importance of Nanoparticle Size, Charge and Surface Chemistry.

The decisive influence on the renal biodistribution is exerted by physicochemical properties. Smaller sized nanoparticles prefer fast filtration and elimination by the urinary system, but larger or aggregated nanoparticles have long circulation and retention in renal tissue. Surface charge changes the interaction with the negatively charged glomerular basement membrane, and the hydrophilic coatings inhibit protein adsorption and tubular uptake. The changes in the surface that are added to add efficacy in the dental properties may hence, occur unintentionally to alter the profiles of renal handling [23].

Table 2. Physicochemical Properties of Nanoparticles Influencing Renal Biodistribution and Clearance

Property	Influence on Renal Handling	Renal Outcome	Key Reference
Particle size	Smaller particles cross glomerular barrier efficiently	Enhanced urinary excretion	[30]
Hydrodynamic diameter	Increased by protein corona formation	Reduced filtration, prolonged circulation	[25]
Surface charge	Cationic particles interact strongly with renal membranes	Increased tubular uptake and retention	[29]

Surface chemistry	Hydrophilic coatings reduce protein adsorption	Improved clearance, reduced accumulation	[23]
Material composition	Metallic nanoparticles show higher surface reactivity	Greater nephrotoxic potential	[28]
Aggregation state	Aggregated particles exceed filtration threshold	Renal retention and accumulation	[26]

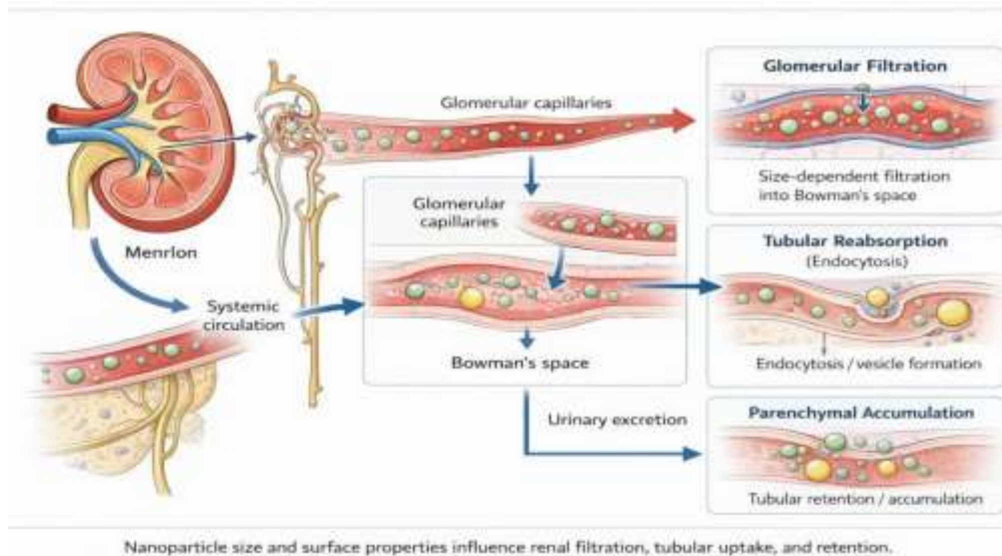

Figure 2. Renal Handling of Nanoparticles: Filtration, Reabsorption, and Accumulation

Schematic representation illustrating nanoparticle transit through glomerular capillaries, size-dependent filtration into Bowman's space, tubular reabsorption via endocytosis, and potential accumulation within renal parenchyma.

5. Systems of Nanoparticle-Induced Renal Toxicity.

The renal toxicity caused by nanoparticles is due to the interaction between man-made nanomaterials and renal cellular and subcellular systems after exposing the body to the nanoparticles. High blood flow, a complicated filtration barrier and tubular epithelium that is metabolically active make the kidney especially vulnerable. Dental therapeutics based on nanotechnology with the potential of systemic diffusion can trigger pathways of renal injury reminiscent of classical druginduced nephrotoxicity and provoke nano-specific pathways regarding size, surface chemistry, and cellular uptake [31].

5.1 Oxidative stress and inflammation

Oxidative stress is one of the major mechanisms in nanoparticle-induced renal injury. Surface redox reaction, mitochondrial interference, and inflammatory cell activation are the mechanisms of generating reactive oxygen species by metallic and inorganic nanoparticles. Over oxidative load interferes with the antioxidant defence mechanisms in renal tubular epithelial cells leading to lipid peroxidation, protein oxidation, and DNA damage. Redox-sensitive transcription signalling increases the release of pro-inflammatory cytokines, which maintain the recruitment of leukocytes and the effects of inflammatory signalling that play a role in progressive renal dysfunction [31].

5.2 Tubular and Glomerular Injury Pathways.

The endocytic activity is high in the renal tubular epithelium which is one of the main points of nanoparticle accumulation. Proximal tubular cells that take up nanoparticles cause cytoskeleton disruption, lysosome instability, and membrane damage. Gomerular injury is caused by interaction of nanoparticles with podocytes and endothelial cells which damage filtration barrier integrity. The changes in the endothelial permeability, slit diaphragm proteins and the basement membrane structure deter selective filtration leading to proteinuria and functional impairment. The effects indicate dose- and exposure-duration dependence in the nanomaterial classes [32].

5.3 Dysfunction and Apoptosis of Mitochondria.

The role of mitochondrial action in the homeostasis of renal cells is significant. Nanoparticles affect electron transport chains of mitochondria, inhibit ATP production, and enhance reactive oxygen species emission. Mitochondrial membrane potential depletion triggers intrinsic apoptotic intrinsic pathways such as cytochrome c release and the activation of caspase. The process of renal apoptotic cell loss stimulates the tube atrophy, fibrosis of the interstitial, and the progressive

renal failure. Re-exposure at low doses continues to sensitize mitochondria as nephrotoxicity is more likely in the longterm [33].

5.4 Metal-Specific and Polymer-Specific Toxic Effects.

Metal nanoparticles exhibit different nephrotoxicity profiles caused by ion release, catalytic surface activity and redox imbalance. Silver, zinc oxide and titanium dioxide nanoparticles emit metal ions that disrupt enzymatic systems and cellular redox homeostasis exacerbating oxidative and inflammatory kidney damage. The imaging studies reveal the presence of nanoparticles in renal compartments, which proves the direct contact with tissues and the possibility of injury [34].Polymeric nanoparticles tend to be less intrinsically toxic in contrast, but the degradation products of the polymer as well as its surface modification and cationic charge can result in immune activation, tubular stress, or kidney irritation. As illustrated in Table 3, the toxicological effects are affected by the molecular weight of the polymer, the degradation rate and the response to renal excretion systems [35].

Table 3. Mechanisms of Renal Toxicity Associated with Commonly Used Dental Nanomaterials

Nanomaterial Type	Primary Renal Toxic Mechanisms	Target Renal Structures	Key Reference
Silver nanoparticles	Oxidative stress, inflammation, ion release	Proximal tubules, glomerular endothelium	[31]
Zinc oxide nanoparticles	Reactive oxygen species generation, apoptosis	Tubular epithelial cells	[32]
Titanium dioxide nanoparticles	Protein corona–mediated accumulation, inflammation	Glomerular filtration barrier	[34]
Polymeric nanoparticles	Endocytic overload, degradationrelated stress	Renal tubules	[35]
Nano-hydroxyapatite	Particle aggregation, mechanical stress	Tubular lumen and interstitium	[33]
Hybrid nanocarriers	Surface chemistry–dependent toxicity	Tubular and vascular compartments	[32]

6. Evidence of Experimental and Preclinical Studies.

The results of experimental and preclinical research allow gaining a necessary understanding of the renal safety profile of nanotechnology dental therapeutics. In vitro and in vivo models allow the systematic study of the interaction of nanoparticles with the kidney, such as dose-effect, effects of exposure duration, and mechanistic pathways of kidney injury. These types of studies are the basis of translational risk assessment and guide the safe clinical incorporation of nanomaterials [36].

6.1 In Vitro Renal Cell Models

The use of in vitro renal cell models, which use proximal tubular epithelial cells, podocytes, and glomerular endothelial cells are the leading platforms through which the cytotoxicity of nanoparticles is investigated. As illustrated in Figure 3, the cell viability, the increase in oxidative stress indicators, and changes in inflammatory signaling pathways are concentration-dependent effects of exposure to metallic and polymeric nanoparticles. Cells of the renal tubules are hyperirritable because of an intense endocytic activity and metabolic load. High-resolution three-dimensional culture devices and co-culture systems also indicate accumulation of intracellular nanoparticles, dysfunction of the mitochondria, and loss of the integrity of the barrier, which reflect earlier cellular processes that lead to a renal injury [37].

6.2 Animal trials that prove the existence of nephrotoxicity.

The biodistribution, renal accumulation, and functional impairment of nanoparticles are present in animal models. The rodent studies have been consistent in showing preferential deposition of nanoparticles in the renal cortex and proximal tubules in cases of systemic exposure. Tubular degeneration, structural change of the glomerulus and interstitial inflammatory infiltration are observed on histopathological examination. Nanoparticles dose and material composition are related to functional indicators such as changes in serum creatinine, blood urea nitrogen, and protein excretion in the urine. The metal-oxide nanoparticles have very high nephrotoxic profiles, especially when exposed repeatedly or in high doses [38].

6.3 Dose-Dependent Effects and Exposure-Duration Effects.

Exposure to nanoparticles in the renal outcomes is highly dependent on the dose of administration and length of exposure. High-dose exposure causes acute oxidative injury and inflammation, and chronic exposure at low dose encourages accumulation and sub-clinical dysfunction of the kidney. Chronic exposure enhances mitochondrial stress, apoptotic signalling and fibrotic pathways of the renal tissue. Experimental results of nanoparticle-based renal therapeutic models

point out that dosing policy and temporality exposure parameters are crucial prerequisites in the regulation of oxidative stress and tissue harm [39].

6.4 Translational Implications of Preclinical Evidence.
Preclinical results reveal that care must be taken in extrapolating the preclinical results to the clinical settings, especially in nanomaterials, where there are chronic exposure situations as in dental therapeutic uses. Although clinical trials of nanoparticle-based systems reveal therapeutic potential, a major therapeutic challenge is still evaluation of renal safety. Systematic review of accomplished clinical trials underlines the necessity of incorporating the preclinical nephrotoxicity information to inform safe human practice [40].

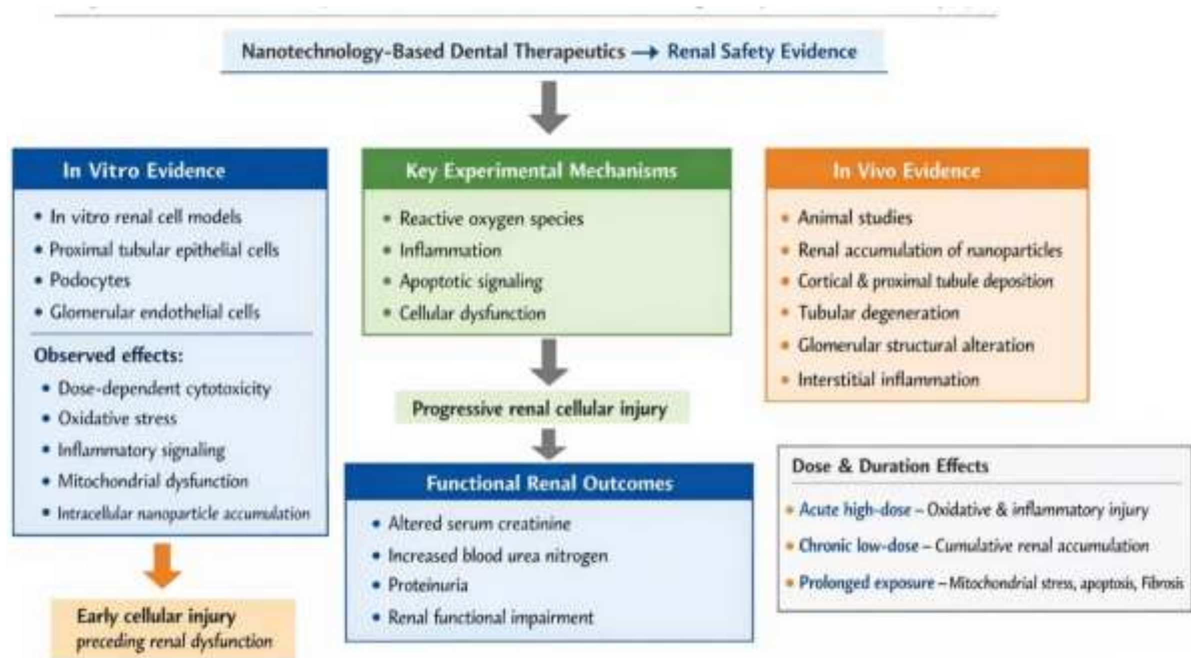

Figure 3. Summary of Experimental Evidence Linking Nanoparticles to Renal Injury

Graphical summary illustrating findings from in vitro renal cell assays and in vivo animal models, highlighting dosedependent cytotoxicity, renal accumulation, oxidative stress, inflammatory responses, and functional impairment following nanoparticle exposure.

7. Clinical/Translational Relevance.
The dental therapeutics based on nanotechnology need to be clinically translated with strict consideration of renal toxicity, especially when used on patients with high risk of nephrotoxic stress. The fact that nanoparticles can interact with cellular and subcellular structures may have disproportionate biological effects even when they are exposed to the body on a low level. According to toxicological data, nanoparticles have the potential to destabilize redox balance, mitochondrial integrity, and inflammatory signaling pathways and thus nephrology-conscious risk mitigation in clinical decision-making is required [41].

7.1 Patient Implication in Chronic kidney disease patients.
The kidney patients who have chronic kidney disease are characterized by decreased glomerular filtration capacity, tubular dysfunction, and decreased susceptibility to oxidative injury and inflammation. Nanoparticles that get into systemic circulation in this group show long circulation in the body and higher chances of collecting in the kidneys. Experimental findings indicate that some nanoparticles such as zinc oxide-based systems cause oxidative stress, mitochondrial damage and apoptosis in epithelial renal tuber cells and such processes have the potential to hasten the onset of kidney functional impairment in damaged kidneys [42]. Nanotherapeutic dental procedures on such a population need thus conservative choice of materials, minimal dosage, and renal biomarker surveillance. The patient should be advised to avoid over the counter (OTC) medications and to reduce alcohol consumption.

7.2 Precautions with Renal Transplant Recipients
Renal transplant patients are a clinically unique patient population, which is immunosuppressed, exhibits modified pharmacokinetics, and is sensitive to inflammatory stimuli. Nanoparticles can also be interplaying with immunosuppressive drugs, the immune signaling mechanisms, and deformative stability of graft microenvironment. Kinetics It is known that clearance kinetics of nanoscale materials can significantly depend on size and surface characteristics and can extend the renal exposure and graft-related risk in transplantation [43]. A multidisciplinary

approach involving the collaboration of dental practitioners and nephrology researchers is thus critical when nanotherapeutic dental materials are involved in transplant patients.

7.3 Drug-Nanomaterial Interactions that can influence the Renal Function.
Nanoparticles have the potential to alter the biodistribution, metabolism, and renal clearance of drugs by adsorption, encapsulation or by competition with the renal transport pathways. The presence of nephrotoxic drugs making the kidney more susceptible to drug toxicity referred to as co-exposure is especially when oxidative stress or uptake of the nanoparticles interacts with pharmacologic burden. As illustrated in Table 4, the literature on nanoparticle-based drug delivery systems show that it could alter plasma protein binding, glomerular filtration properties, and tubular secretion, and its impact is essential in the clinical planning of drugs-nanomaterial interactions [44]. Silver nanoparticle-containing dental material also deserves a warning as it is observed to have systemic reactivity and accumulation [45].

Table 4. Renal Risk Considerations of Dental Nanotherapeutics in Vulnerable Patient Populations

Patient Population	**Renal Risk Factors**	**Clinical Considerations**	**Key Reference**
Chronic kidney disease	Reduced clearance, oxidative vulnerability	Material selection, exposure minimization, renal monitoring	[42]
Renal transplant recipients	Immunosuppression, graft sensitivity	Interdisciplinary coordination, cautious material use	[43]
Elderly patients	Age-related renal functional decline	Conservative application, cumulative exposure assessment	[41]
Patients on nephrotoxic drugs	Combined renal burden	Evaluation of drug–nanomaterial interactions	[44]
Patients exposed to silver nanoparticles	Systemic reactivity, accumulation risk	Avoidance highly reactive nanomaterials	[45]

8. Less Toxic Nanomaterial and Nephroprotective Strategies.
The further development of nanotechnology-based dental therapeutics requires the simultaneous development of nephroprotective measures that would reduce the toxicity and renal exposure. Renal safety implemented during material design promotes the alignment of material design with clinical priorities and changing regulatory requirements in nephrology. Engaging safer nanomaterial engineering focuses on physicochemical optimization, regulated biodistribution, and alleviation of biosafety stress on cells found in the kidney to minimize the risk of nephrotoxicity [46].

8.1 The modification of surfaces and biocompatible coating
Surface engineering is a key factor that will ensure that nanoparticle-kidney interactions are altered through changes in biological identity and circulation behavior. Nonspecific protein adsorption and immune recognition are prevented by biocompatible coatings, including polyethene glycol, polysaccharides and zwitterionic polymers, which reduces the formation of protein corona. These changes decrease the renal tubular uptake and inflammatory activation without eliminating the antimicrobial or regenerative effects in dental practice. The properties of stability and degradation of surface coatings also have an additional impact on systemic persistence and duration of renal exposure [47].

8.2 Size and Charge Optimization
The size and surface charge of nanoparticles is of great significance in defining renal filtration and tissue retention. Optimization of nanoscale sizes of the particles that are engineered leads to clearance and reduced renal retention in the long term. Weakly negatively charged surface charge or a neutral charge decrease contact between the negatively charged glomerular basement membrane and tubular epithelial surfaces. The size and selectivity of glomeruli under experimentally relevant conditions are shown to be supported by the nephroprotective benefit of charge-sensitive nanomaterials, especially in repeated or long-term exposure conditions typical of dental therapy [48].

8.3 Controlled Release Systems
The controlled release nanocarriers lower the peak levels in the systemic circulation by administering therapeutic agents in a controlled and localized way. These systems reduce the chances of acute renal exposure and subsequent nephrotoxicity by reducing the burst release. Controlled release formulations are also useful in periodontal and implantbased therapies to help increase the local efficacy and reduce the systemic dispersion. Slow deterioration and maintenance of kinetics in release counteract progressive renal load and facilitate safety in the long term [49].

8.4 Renal Safety-by-Design Approaches.
Renal safety-by-design entails the evaluation of nephrotoxicity into the early phases of nanomaterial development, as opposed to post hoc evaluation. In this model, predictive modelling, physicochemical profiling, and in vitro renal screening are used to determine those materials that possess adverse renal handling properties before clinical testing. Optimization of dental performance and nephroprotection can be balanced with the help of iterative refinement based on renal-specific safety endpoints. Implementation of safety-by-design measures is consistent with principles of responsible nanotechnology regulation and can be used to facilitate sustainable clinical translation [50].

9. Regulatory, Toxicological and Risk-Assessment Perspectives.
The current clinical trend in the increasing number of dental therapies based on nanotechnology raises concerns about the need to have a sound regulatory framework and thorough renal safety assessment. Even though there are some regulations frameworks that give a general direction on quality, safety, and efficacy, kidney specific considerations are not well incorporated. The functionality, composition, and physicochemical variability of nanoparticles on the surface of the nanoparticles play a significant role in determining systemic toxicity and hence the relevance of organ-targeted risk assessment approaches [51].

9.1 Existing Regulatory Frameworks of Nanomaterials.
Regulatory bodies identify nanomaterials as unique substances that demand special consideration because of the effect they have based on their nano state. Recent models focus on physicochemical characterization, consistency in manufacturing, and overall toxicity testing when developing a product. Manufacturing and analytical viewpoints are concerned with reproducibility, quality management and systematic exposure estimation but those renal endpoints are usually incorporated into generalized toxicity experiment instead of being tackled separately [52]. Consequently, dental nanotherapeutics with specific toxicokinetic behaviour towards the kidney can be under characterised.

9.2 Gaps in renal safety Evaluation.
Current paradigms in toxicology fail to explain nanoparticle-specific mechanisms of renal injury. Conventional and standard tests focus on acute toxicity and apparent histopathologic injury, whereas minor alteration in tubular function, stress of the mitochondria and oxidative stress may remain unseen. Specifically, metal and metal oxide nanoparticles trigger the toxicity caused by the oxidative stress that develops over time and is not necessarily revealed during shortterm testing [15]. Further, nanoparticles size, surface chemistry, and aggregation state can vary, which would not ease comparison of cross-studies and extrapolate evidence to nephrology practice [53].

9.3 Standardization of Nephrotoxicity Screening Requirement.
Nanomaterial-specific standardized protocols of nephrotoxicity screening are needed to facilitate regulatory assessment and clinical safety in Table 5. The strategies involve alternative and predictive testing methods that use in vitro models of kidney renal stress, high-content screening, and predictive biomasses to detect renal stress induced by nanoparticles early. Standardization of testing procedures enhances consistency and regulatory articulation and lowers the application of latestage animal experiments [54]. Use of kidney-centered endpoints enhances translational utility and harmonization of nanotherapeutic development towards the ideals of nephrology practice [55] .

Table 5. Regulatory and Safety Evaluation Requirements Relevant to Nanotechnology and Renal Health

Evaluation Domain	Current Regulatory Focus	Renal-Relevant Considerations	Key Reference
Physicochemical characterization	Size, shape, surface chemistry	Prediction of renal filtration and accumulation	[51]
Systemic toxicity testing	Acute and subacute exposure	Inclusion of tubular and glomerular endpoints	[15]
Biodistribution assessment	Organ-level accumulation	Quantitative renal uptake and clearance	[44]
Long-term safety evaluation	Limited chronic exposure data	Cumulative renal toxicity assessment	[53]
Risk assessment frameworks	Generalized toxicity models	Kidney-specific risk stratification	[54]
Post-market surveillance	Adverse event reporting	Renal function monitoring in exposed populations	[55]

9.4 Translational and Material-Specificities.
In addition to regulatory framework, design decisions that rely on materials have an impact on safety assessment routes. Dental nanotherapeutics containing silver nanoparticles or polymer nanoparticles are antimicrobial effective but should

be evaluated with caution since they are systemically reactive and prone to long-term exposure [56]. Though often characterized by enhanced biocompatibility, polymeric nanoparticle systems, nevertheless, require renal-oriented assessment owing to degradation products and long-circulation curves [57]. The association of the properties of nanomaterials with the biological effects of toxicity contributes to the fine-tuning of risk-assessment and safer clinical translation [58].

CONCLUSION

Nanotechnology dental therapeutics provides a major change in the contemporary oral health care wherein it provides better antimicrobial effect, better quality of the material and local delivery of therapy. But there is an increasing amount of evidence that nanoscale materials utilized in dental practice could be absorbed but exposed via various pathways through the body into systemic circulation, becoming involved in the renal system of filtration and clearance. The high perfusion rate of the kidney and the specialized glomerular and tubular system of the kidney make the kidney a critical organ in the nanoparticle handling as well as a possible location of cumulative exposure. As evident in experimental and preclinical literature, oxidative stress, activation of inflammation, dysfunction of mitochondria, and injury to the tubule are some of the major mechanisms underlying nanoparticle-linked renal effects. Although these results give the potential clinical safety issues, it is limited to human risk assessment due to limited long-term clinical data, especially in the population already having renal impairment. This would provide more than enough to argue that future clinical testing of dental nanotherapeutics should be conducted with extended observational studies and kidney-centered endpoints. It is, therefore, necessary to integrate dental nanomedicine development with principles of nephrology. The interdisciplinary approach will be able to inform safer material design, predict patient-related risk classification, and regulatory frameworks capable of operating organ-specific organ toxicity. With the consideration of renal safety and the way to align innovation in the dentistry field, future studies can facilitate responsible clinical translation and protect vulnerable groups of patients.

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