Biological Trace Element Research (2020) 197:70–88
https://doi.org/10.1007/s12011-019-01986-y

Nanometals in Dentistry: Applications and Toxicological Implications—a Systematic Review

Rupali Agnihotri[1] · Sumit Gaur[2] · Sacharia Albin[3]

Received: 7 August 2019 / Accepted: 14 November 2019 / Published online: 28 November 2019

Abstract

Nanotechnology is a vital part of health care system, including the dentistry. This branch of technology has been incorporated into various fields of dentistry ranging from diagnosis to prevention and treatment. The latter involves application of numerous biomaterials that help in restoration of esthetic and functional dentition. Over the past decade, these materials were modified through the incorporation of metal nanoparticles (NP) like silver (Ag), gold (Au), titanium (Ti), zinc (Zn), copper (Cu), and zirconia (Zr). They enhanced antimicrobial, mechanical, and regenerative properties of these materials. However, lately, the toxicological implications of these nanometal particles have been realized. They were associated with cytotoxicity, genotoxicity altered inflammatory processes, and reticuloendothelial system toxicity. As dental biomaterials containing metal NPs remain functional in oral cavity over prolonged periods, it is important to know their toxicological effects in humans. With this background, the present systematic review is aimed to gain an insight into the plausible applications and toxic implications of nano-metal particles as related to dentistry.

Keywords Antimicrobial · Dentistry · Nanotechnology · Nanometals · Toxicity

Introduction

Metals are an integral component of various dental restorative and prosthetic materials. Their mechanical properties like elastic modulus, tensile strength, and hardness confer strength and durability to the dental restorations and prostheses, when exposed to functional loads in the oral cavity [1]. The metals applied in dentistry include both noble (e.g., gold (Au), silver (Ag), palladium (Pd), and platinum (Pt)) and base metals (e.g. copper (Cu), zinc (Zn), titanium (Ti), nickel (Ni), chromium (Cr), zirconium (Zr), beryllium (Be), boron (B), and aluminum (Al)) [2]. They may be used alone or in the form of alloys, for restorative and prosthetic purposes.

✉ Sumit Gaur
get2sumitgaur@yahoo.co.in; sumit.gaur@manipal.edu

[1] Department of Periodontology, Manipal College of Dental Sciences, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka 576104, India

[2] Department of Pedodontics and Preventive Dentistry, Manipal College of Dental Sciences, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka 576104, India

[3] Engineering Department, Norfolk State University, Norfolk, VA 23504, USA

Lately, nanoparticles (NPs) of metals or their compounds have been incorporated into the dental restorative materials, pulp capping agents, denture-base materials, implants, orthodontic appliances, and oral hygiene aids [3]. Besides improving their physiochemical and mechanical properties, the NPs of metals like Ag, Cu, Au, Ti, and Zn are antibacterial in nature. Therefore, they may be helpful in inhibiting the dental plaque biofilm. In orthodontics, the NP-coated arch wires, adhesives, elastomeric ligatures, temporary anchorage devices, orthodontic wires with shape memory and biofilm control features, and nanometal-coated brackets have been applied [4]. Among them, the NPs of Ag, Au, ZrO_2, and TiO have been added to the orthodontic adhesives to increase their compressive, tensile, and shear bond strengths [5, 6]. The NPs of Ag, Cu, and Zn produce an antibacterial and antibiofilm effect when coated on orthodontic brackets [7]. They have also been applied on the stainless steel arch wires to reduce the frictional forces between the wires and the bracket [4, 8].

These NPs are less than 100 nm in diameter which increases their ratio of surface area to volume, chemical reactivity, and biological activity [9]. Their antibacterial effect is mainly attributed to the former and metal-ion release [10]. They even generate reactive oxygen species (ROS) that react with the microbial membranes, damage their structure, and inactivate the bacteria. Furthermore, their unusual crystalline

morphologies with a high number of edges and corners, and other potentially reactive sites increase their antibacterial effect [10].

Although metal NPs have better mechanical properties and esthetic outcomes, little is known about their toxicological aspects when functioning for a long time in a living organism [11]. This is specifically true for the restorations incorporating NPs as they may undergo dissolution in the saliva or chemical or physical destruction, erosion from food, wear by chewing, bacterial activity, and variations in temperature and pH [12, 13]. Subsequently, the metal ions released into the oral cavity may enter into systemic circulation through oral fluids and blood vessels. They may be taken up by the cells due to their small particle size and may be localized, undergo degradation and exocytosis [14]. Conversely, they may cause cytotoxicity, genotoxicity, and inflammatory responses [15]. The severity of these reactions is dependent on the size, shape, surface chemistry, and the cell types exposed to the metal ions [15].

As the nanometals have been recently introduced in dentistry and are widely incorporated for improving the antimicrobial and mechanical properties of various dental materials, the present review aims to gain an insight into the applications of nanometals in dentistry. It also describes the plausible toxic implications of these nano metal particles on oral and general health.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed to identify the research publications on applications of nanometals and their oxides in dentistry. Further, articles related to their adverse effects on oral health were also searched. The databases searched were Medline (PubMed), Scopus, and Web of Science. A combination of keywords like “Nanometals” OR “Nano” OR “Silver” OR “Titanium” OR “Gold” OR “Platinum” OR “Palladium” OR “Zinc” OR “Copper” OR “Zirconia” OR “Nickel” OR “Oxides” OR “Toxicity”, AND “Dentistry” were used. They were verified in the titles, abstracts, or keywords during the initial search. It resulted in a total of 572 articles (Fig. 1). The data was screened for duplicates which resulted in 507 articles wherein the titles and abstracts were read. The eligibility criteria were free full-text original articles in English language related to the applications and toxicity of the above nanometals and their compounds in dentistry. Only articles published from 2009 to 2019 were included. Any kind of recommendations, expert statements, reviews, technical reports, case reports, and non-original papers were excluded. Furthermore, only studies reporting incorporation of NPs of metals in the dental materials were included. This resulted in 104 original research articles of which 49 were excluded after reading the full text. Finally, full texts of 55 original studies have been included in the review [16–67]. The nanometals used in the dental material, the type of dental material, their surface characterization, size, concentration, mechanism of action and toxic effects, if any, were recorded (Tables 1 and 2).

Results

Of the 55 studies that were included in the review, 48 reported the applications of nano metals in dentistry. Among them 42 were in vitro studies, 2 were animal studies while 4 were randomized controlled clinical trials [16–61]. About 5 in vitro and 1 animal study investigated the toxic implications of nanometals used in various dental materials [62–67]. The following sections discuss the applications and toxic implications of the nanometals used in dentistry.

Applications of Nanometals in Dentistry

In dentistry, the applications of nanometals range from diagnosis to preventive and therapeutic purposes (Fig. 2). As already stated, they improve the mechanical properties and confer antimicrobial activity to the different materials (Fig. 3). Their applications in dentistry as reported in various studies are summarized as follows (Table 1):

a. Nanometals used in various dental materials

The most common nanometals used in the dental materials were Ag, Ti, Cu, Au, Zn, and Zr [16–61]. The Ag and Au were used in their pure form while the nano-oxides of Ti, Zn, Cu, and Zr were employed more often [16–61]. They were incorporated in the composite resins, acrylic denture base resins, endodontic materials, dental implants, restorative cements, and orthodontic brackets and adhesives where they showed improved antimicrobial, mechanical, and regenerative properties which would be discussed in the later section [16–61]. The nanometal particles were incorporated into the following dental materials:

i. Restorative materials

The restorative materials like composite resins produce excellent esthetics and load-bearing properties but often undergo failure due to biofilm accumulation, secondary caries, and bulk fracture [68, 69]. Likewise, inadequate instrumentation or microleakage in the filled root canals results in treatment failure [70]. The NPs of Ag, ZnO, and Zr were added to composite resins, cavity varnishes, glass ionomer cement (GIC’s), intracanal medicaments (e.g., calcium hydroxide [Ca $(OH)_2$]), sealers, and root end materials (e.g., Portland

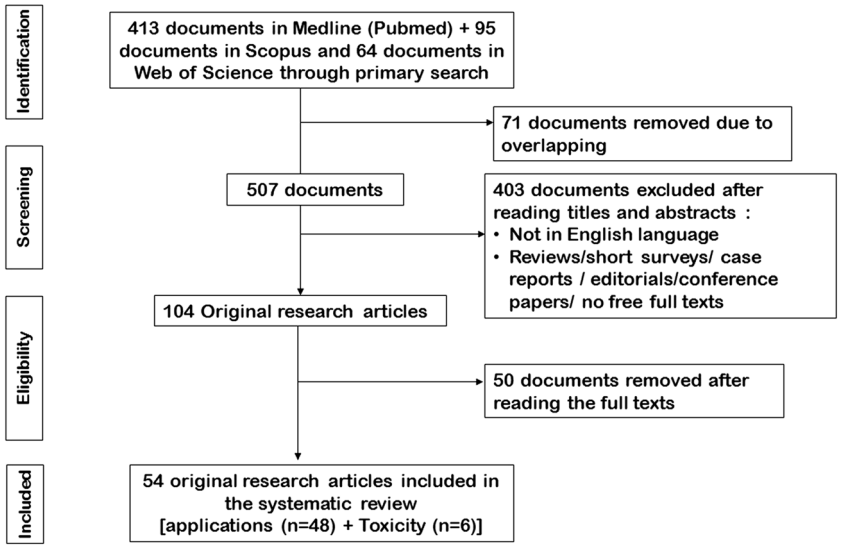

Fig. 1 Evidence search on applications of nanometals in dentistry and their toxic implications

cement and mineral trioxide aggregate (MTA)) to overcome these problems [16–37].

ii. Prosthodontic materials and dental implants

The full mouth rehabilitation for the lost teeth is usually done with the help of acrylic partial/complete dentures or dental implants. The dentures are made of poly methyl metha acrylate (PMMA) resin which has a rough inner surface that favors biofilm accumulation [71]. It promotes colonization by *Candida* that causes denture stomatitis, specifically in elderly [72]. The dental implants, although a predictable method for oral rehabilitation may undergo failure due to mechanical (e.g., static and dynamic occlusal load) and biological (e.g., biofilm accumulation and invasion) factors [73, 74]. In order to overcome these problems, NPs of Ag, ZrO_2, and TiO_2 were added to the PMMA or coated on the surfaces of dental implants [38–57]. They improved their antimicrobial and mechanical properties as well as favored osseointegration and soft-tissue healing around the dental implants [51–57].

iii. Orthodontic appliances

The orthodontic treatment is often complicated due to the development of white-spot lesions and dentinal caries. The orthodontic brackets act as plaque retentive factors that promote biofilm formation, proliferation of the facultative bacteria, reduced pH, and enamel demineralization [75]. The addition of NPs of Cu and Zn oxides to orthodontic brackets inhibited plaque biofilm and produced an anti-caries effect. Besides increased biofilm formation and caries, frequent debonding of the orthodontic brackets often prolongs the treatment time [6]. This was attributed to reduced bond strength of the orthodontic adhesives used to bond the brackets to the tooth surface. The nanofillers of Zr and Ti oxides were added to improve the bond strength [7, 58].

iv. Other applications

Some other uses of nanometal particles include oral diagnosis whereby the NPs of Au, Ag, Pt, and Pd were incorporated into the nanobiosensor transduction/bioreception systems. These NPs rapidly reacted with most biological molecules. The NPs of Au specifically enhanced the electronic signals when the analyte was at very low concentrations [76]. They were applied on toothbrushes along with the AgNPs where they enhanced the effects of mechanical plaque control owing to their antibacterial action. This helped in better reduction of periodontal diseases [76]. The AgNPs have also been added to the anticaries components of dentifrices like calcium glycerophosphate [59, 60].

b. Surface characterization of nano metal particles in various dental materials

The surface characterization enables determination of size, shape, concentration, and dispersion of the nanometals in various materials. In the research reviewed here, the physical characteristics of metals were analyzed through transmission electron microscopy (TEM), X-ray photon spectroscopy, scanning electron microscopy (SEM), dynamic light scattering, inductively coupled plasma-optical emission spectrometry, UV–Vis spectroscopy, X-ray diffraction, atomic force microscopy, X-ray photon spectroscopy, and field-emission scanning electron microscopy [7, 18, 19, 21, 23, 27, 30, 31, 38, 44–49, 51–53, 55–57, 59–61]. Among them, the TEM was most commonly applied [7, 18, 21, 30, 31, 42, 51, 55, 56, 60]. They revealed the following characteristics of the nano metal particles:

Table 1 Applications of nano metals and their compounds in dentistry

Dental application	Nano metal particle applied	Antimicrobial efficacy	Mechanical properties evaluated	Regenerative effects	References		
					In vitro studies	In vivo studies	Animal Studies
Restorative materials	Ag ZnO TiO_2 Au ZrO_2	*S. mutans* *E. faecalis* *P. aeruginosa* *E. coli* *S. aureus* *Lactobacillus*	Shear bond strength Microleakage Apical seal Flexural strength Compressive strength Surface micro hardness Radiopacity	• AuNPs promoted osteogenesis • ZrO2 caused inflammatory reaction and promoted fibroblast proliferation	Cheng L et al. 2013 [16] Zhang K et al. 2013 [17] Rad MS et al. 2013 [18] Dugal S et al. 2014 [19], Kasraei S et al. 2014 [20] Javidi M et al. 2014 [21] Aguiar AS et al. 2015 [22] Garcia-Contreras R et al. 2015 [23] Cheng L et al. 2016 [24] Teymoornezhad K et al. 2016 [25] Afkhami F et al. 2016 [26] Ibrahim MA et al. 2017 [27] Nozari A et al. 2017 [28] Scarpelli BB et al. 2017 [29] Paiva L et al. 2018 [30] , Xia Y et al. 2018 [31]	Santos VE Jr et al. 2014 [32] Ghorbanzadeh R et al. 2015 [33] Freire PLL et al. 2017 [34] Tirupathi S et al. 2019 [35]	Silva GF et al. 2014 [36] Silva GF et al. 2017 [37]
Prosthodontic materials	Ag TiO_2 Zr ZrO_2	*C. albicans*, *Lactobacillus* *S. mutans* *C. scotti*	Tensile strength Transverse strength Flexural strength Impact strength Surface hardness Fracture toughness Translucency Wear resistance		Suganya S et al. 2014 [38] Ghaffari T et al. 2015 [39] Li Z et al. 2016 [40] Sodagar A et al. 2016 [41] Gad M et al. 2016 [42] Gad M M et al. 2016 [43] Totu EE et al. 2017 [44] Alhavaz A et al. 2017 [45] Elias CN et al. 2017 [46], Ergun G et al. 2018 [47], Gad M M et al. 2018 [48], Darwish G et al. 2019 [49] Gad M M et al. 2019 [50]		
Dental implants	Ag Ti, TiO_2 ZnO Au	Planktonic Bacteria *S. sanguinis* *A. naeslundii* *C. albicans* Facultative anaerobes *Streptococcus* *S. aureus*	-	• Osteoconduction • Platelet activation & aggregation • Osseo integration • Cell proliferation & differentiation	Zhao L et al. 2011 [51] Fröjd V et al. 2011 [52] Huang HH et al. 2012 [53] Matsubara VH et al. 2015 [54] Abdulkareem EH et al. 2015 [55] Memarzadeh K et al. 2015 [56]		Heo DN et al. 2016 [57]
Orthodontic appliances	ZnO CuO ZrO_2 TiO_2	*S. mutans*	Compressive Strength Tensile strength Shear bond strength		Felemban NH et al. 2017 [6] Ramazanzadeh B et al. 2015 [7] Toodehzaeim MH et al. 2018 [58]		
Dentifrices	Ag Zn	*C. albicans* *S. mutans*	Dentin remineralization Tubular occlusion		Fernandes GL et al. 2018 [59] Teixeira JA et al. 2018 [60] Toledano-Osorio M et al. 2018 [61]		

Table 2 Evidence related to toxicity of nano metals used in dental materials

Author	Aim of the study	Type of study	Nano metal evaluated for toxicity	Salient features	Results and conclusions
Heravi F et al. 2013 [62]	Investigated cytotoxicity of orthodontic adhesive containing 1 wt% TiO_2 NPs	In vitro	TiO_2 NPs	• Ten composite disks prepared from conventional and TiO_2 containing composites were aged for 1, 3, 5, 7 and 14 months • The extracts were obtained and exposed to culture media of human gingival fibroblasts (HGF) and mouse L929 fibroblasts. • Cell viability was measured	• Both adhesives → moderate toxicity to HGF cells on the first day • Significantly lower toxicity with TiO_2 NP adhesive • On other days, no significant differences in cell viability percentages between the two groups • Increased pre-incubation time → significant reduction in cell toxicity • L929 cells showed similar toxicity trends, but lower sensitivity • The TiO_2 NPs adhesive had lower toxicity than control • Incorporation of 1 wt% TiO_2 NPs → no additional health hazard
Garcia-Contreras R et al. 2014 [63]	Investigated the possible cytotoxicity and pro inflammation effect of three different powdered GICs (base, core build and restorative) prepared with and without TiO_2 NPs	In vitro	TiO_2 NPs	• The GIC was blended with TiO_2 nanopowder, anatase phase (< 25 nm; 3% and 5% (w/w)) • Human oral squamous cell carcinoma cell lines (HCS-2, HSC-3, HSC-4, Ca9-22) and human normal oral cells [gingival fibroblast (HGF), pulp (HPC) and periodontal ligament fibroblast (HPLF)] were incubated with different concentrations of GICs in the presence or absence of TiO_2 NPs • The viable cell number, Prostaglandin E2 levels & changes in cell structure were assessed	• Cancer cells exhibited moderate cytotoxicity after 48 h of incubation, regardless of the type of GIC and the presence or absence of TiO_2 NPs • GIC induced much lower cytotoxicity but induced Prostaglandin E2 and interleukin-1β in normal cells • Acceptable to moderate biocompatibility and proinflammatory effects of GICs impregnated with TiO_2 NPs
Chan EL et al. 2015 [64]	Evaluated the cytotoxic effect of a novel AgNP endodontic irrigant and compared with 3% sodium hypochlorite	In vitro	AgNPs	• The study included evaluation of direct and indirect effects on mouse fibroblasts (NIH 3T3) and primary human periodontal ligament stem cell (hPDLSCs) when exposed to the two solutions	• AgNP irrigant was non-cytotoxic to both NIH 3T3 and hPDLSCs
Zand V et al. 2016 [65]	Evaluated the subcutaneous inflammatory reaction of rat connective tissues to white MTA with and without AgNPs	Animal study	AgNPs	• The experimental materials (MTA and MTA+NS and empty control tubes) were implanted in subcutaneous tissues of 75 male rats • Animals (n = 15) were divided into five groups: group 1 (after 7 days), group 2 (after 15 days), group 3 (after 30 days); group 4 (after 60 days) and group 5 (after 90 days) • The inflammatory reaction was graded	• No significant difference in the inflammatory reactions between the groups • Incorporation of 1% AgNPs to MTA does not affect the inflammatory reaction of subcutaneous tissue in rat models

Table 2 (continued)

Author	Aim of the study	Type of study	Nano metal evaluated for toxicity	Salient features	Results and conclusions
Akay C et al. 2018 [66]	Evaluated the cytotoxicity of different kinds of NPs added to two types of maxillofacial elastomers	In vitro	TiO_2 NPs	• A-2000 and A-2006 silicone elastomers were used and the silicone specimens were divided into eight groups according to the presence of additional NPs.	• TiO_2 NPs, fumed silica, and silaned silica added to a commercial silicone-based elastomer were nontoxic
Laiteerapong A 2019 [67]	Formulated and investigated the genotoxic effect of novel GICs containing ZrNPs and micro-particles on DNA double-strand breaks of human gingival fibroblasts (HGFs)	In vitro	ZrO_2 NP	• GIC (control), 10%ZrO_2NPs + GIC and 10%ZrO2 microparticles + GIC were prepared • A H2AX immunofluorescence assay was per-formed to evaluate double-strand breaks of HGFs	• GIC and both Zr modified GICs had no genotoxic effect on HGFs

i. Size

The size, shape, and structure of NPs affects the reactivity, toughness, and other qualities including the optical properties of dental materials. This is significant for materials related to dental aesthetics like composite resins and denture bases. The size of NPs affects the color of these materials due to absorption of light in the visible region.

The size of nanometals ranged from 5 to 260 nm [30, 46]. The average size of AgNPs was between 5 and 100 nm [30, 38, 42]. The nano TiO_2 particle size ranged from 10 to 93 nm [51, 53]. Likewise, the size of nano ZnO particles ranged from 20 to 225 nm [55, 61]. The particle size of nano CuO was 37 nm while that of Au was about 18 nm [7, 31]. The particle size of nano Zr and its oxide ranged from 40 to 830 nm [43, 46].

ii. Shape and dispersion

The nanometals were mostly spherical in shape [21, 23, 25, 30, 31, 44, 59–61], although one study reported triangular configuration [19]. They were evenly dispersed in all the dental materials [19, 21, 23, 25, 30, 31, 49, 59–61].

iii. Concentration

The concentration of the NPs varied according to the property of the material which was enhanced, i.e., antimicrobial or mechanical properties. For instance, the AgNPs were commonly used in concentration of 0.1 to 1 w/w% in the composite resins where they produced antibacterial effect and improved their flexural strength, elastic modulus, and shear bond strength [16, 24]. They produced antibacterial effect in bonding agents at 0.05 to 0.1w/w% concentration [16, 17] while the antifungal effect was seen when they were incorporated in the denture base resins at concentrations 2.5, 3 and 5w/w% [38–40]. In dental implants antifungal effect was produced at a concentration of 320 ppm [54]. They augmented the antibacterial effect of GICs, intracanal medicaments and dentifrices at concentrations 0.5w/w% [30], 100 ppm concentration [26] and 200 ppm [59], respectively. They increased the surface hardness of a cavity varnish at a concentration of 376.5 μg/ml [28].

The CuO NPs were incorporated in the concentrations 0.01, 0.5, and 1w/w% in the orthodontic adhesive. They enhanced its antibacterial property and shear bond strength [58]. Likewise, 3 to 5w/w% of TiO_2 NPs improved the flexural and compressive strengths of GICs [23, 27]. In denture base resins, at 0.4, 0.5 and 1w/w% concentration, these NPs produced antibacterial and antifungal effects [41, 44].

In endodontic sealers and dental implants, the ZnO NPs were used either alone or in combination with Ag and TiO_2 NPs to enhance their antimicrobial and mechanical properties [18, 55, 56]. They had a similar effect on composite resins, at 1 and 3w/w% concentrations [20, 25]. The nano Zr and its oxide

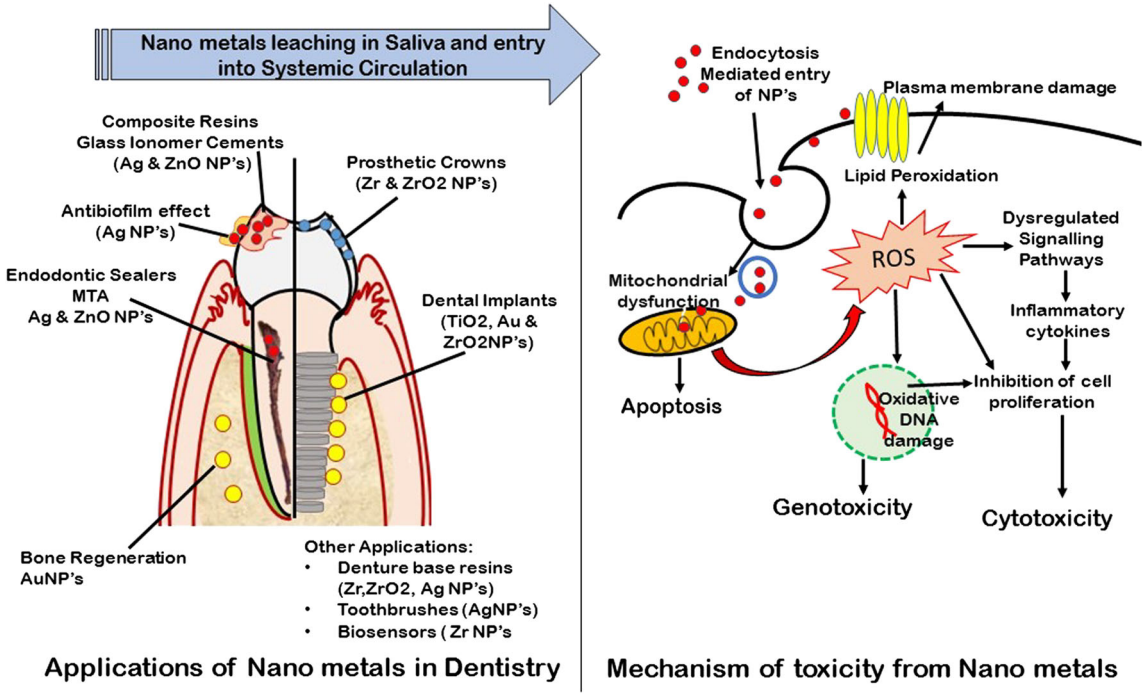

Fig. 2 Applications of nanometals in dentistry and mechanism of their plausible toxicity

were widely used in denture base resins, ceramics and restorative cements [6, 36, 37, 42, 43, 45–48, 50]. Their concentration varied from 1 to 20 w/w% in denture base resins, 30 w/w% in Portland and calcium silicate cements and 0.5 to 1w/w% in orthodontic adhesives [6, 36, 37, 42, 45, 47, 48]. The Zr NPs mainly enhanced the mechanical properties of these materials.

c. Synthesis and methods of incorporation of nano metals in the dental materials

The nano metal particles may be synthesized by a top down or a bottom up approach (Fig. 3). The former includes lithographic techniques and etching while the latter consists of sputtering, chemical vapor deposition, sol–gel processes, spray pyrolysis, laser pyrolysis, and atomic/molecular condensation [77]. Lately, a "green synthesis" approach utilizing biological microorganisms like bacteria, fungi, algae, yeast, and plant extracts has been developed to obtain the NPs of metals like Au, Ag, Zn, and ZnO [77].

However, the studies included in this review utilized commercially available and chemically formulated nanometal particles [6, 20, 26, 39, 40, 58]. The AgNPs were prepared by the reduction of silver nitrate ($AgNO_3$) with sodium borohydride, sodium citrate, or ethylene glycol [19, 38, 59, 60]. Besides, photoreduction was also applied on a mixture of $AgNO_3$, tartaric acid, and PAA to obtain them [30]. A mixture of $AgNO_3$ and zinc nitrate ($ZnNO_3$) in gelatin was calcined at different temperatures to obtain ZnO: Ag composite NP powder, which was used as an endodontic sealer [18].

The AgNPs were incorporated with the help of a monomer, 2-(tert-butylamino) ethyl methacrylate (TBAEMA) in the polymeric dental material. This agent improved the solubility of Ag ions in the resin solution and its reactive methacrylate groups integrated with the polymer network upon photopolymerization [16, 17, 19, 24].

The AuNPs were synthesized by the reaction between the chloroauric acid trihydrate and sodium citrate. This resulted in a colloidal solution of AuNPs which was mixed with the calcium phosphate cement [31]. Likewise, a nano thickness film of TiO_2 synthesized through the reaction between tetrakis (dimethylamido) titanium (TDMAT) and ozone was deposited on titanium implants using atomic layer deposition (ALD) technique [49]. Additionally, the TiO_2 NPs were prepared through a modified sol-gel procedure utilizing titanium tetrabutoxide Ti (OBu) 4 and dimedone as a chelating agent. Some studies included commercially available TiO_2 nanopowder in anatase phase [23, 27, 41, 44].

Both commercially available ZnO NPs as well as those synthesized by a modified sol-gel method from gelatin and $ZnNO_3$ at high temperatures (500–700 °C) were used [21, 22, 25]. They were also synthesized from $ZnSO_4$ and $ZnCl_2$ [7, 61]. The CuO NPs were prepared by a reaction between copper acetate, glacial acetic acid, and sodium hydroxide [7]. It resulted in a black precipitate of CuO from which NPs were obtained.

The commercially available ZrO_2 NPs (99.9% pure) were incorporated into the PMMA resin, orthodontic adhesives, ceramic restorations, and Portland and calcium silicate cements [6, 36, 37, 42, 43, 45–48, 50]. They were subjected to

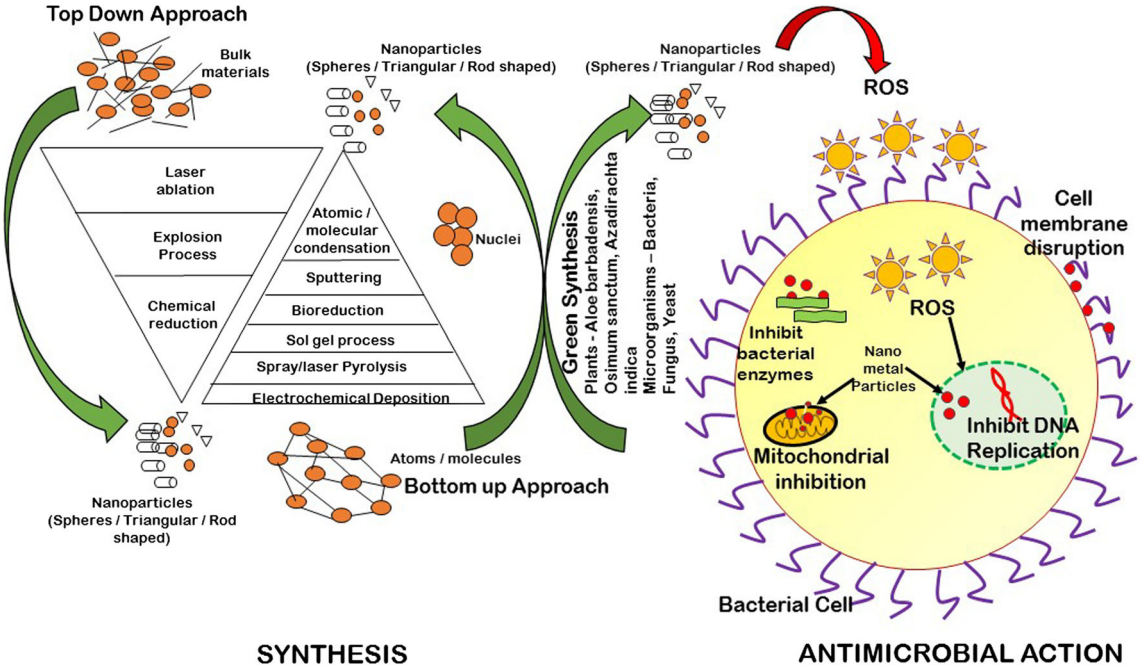

Fig. 3 Synthesis and antimicrobial effect of nanometals used in dental materials

salinization process (addition of a silane coupling agent, 3-(trimethoxysilyl) propyl methacrylate (TMSPM) to ZrO_2) which rendered their surface reactive and enabled adequate adhesion between the NPs and the resin matrix.

In the dental implants, the AgNP suspensions were either directly deposited on their inner cavity or applied on the surfaces of the titania nanotubes, by soaking the titanium disks in $AgNO_3$ solutions followed by UV light irradiation from a high-pressure Hg lamp [51, 54]. Furthermore, the chemically synthesized AuNPs were deposited on the silanized Ti surface with the help of Au-S bonding. The TiO_2 NPs were deposited with the help of a sol gel or anodic treatment and the ZnO NPs (prepared by flame pyrolysis) were deposited with the help of electro hydrodynamic spraying on the dental implants [52–56].

d. The biological and mechanical effects of nanometals used in dental materials

The nanometals and their compounds are very similar to atoms due to their nanoscale size. This enables interactions at molecular levels in the biological tissues that surpasses those of micro- or macro-sized particles [76, 78, 79]. They are highly reactive as free surface atoms can form new and strong bonds and also allow the manipulation of NPs in a number of packing configurations [76, 79]. They have a low melting temperature due to high thermal vibrations of surface atoms in comparison with the core atoms [76, 80]. This is specifically useful in constructing porcelain fused to metal crowns, cast post and cores, or denture frameworks [76].

The following properties of nano metal particles were observed in the reviewed literature that make them ideal for use in dental materials:

i. Antimicrobial property

In the present review, the Ag NPs were the most commonly applied antimicrobial nano metals followed by TiO_2, Zn, ZnO, and CuO [7, 16–20, 22–24, 26, 27, 29, 30, 32, 34, 35, 38, 40, 41, 44, 49, 51–56, 58–60]. The bactericidal activity of nanometals is dependent on their size and shape [73] (Fig. 3). A study reported that smallest nano metal particles with spherical configuration were more bactericidal than the triangular and larger spherical shaped particles [73]. As already stated, in most of the studies the shape of the nano metal particles was spherical and their size ranged from 5 to 260 nm [19, 21, 23, 25, 30, 31, 44, 59–61].

In composite resins, PMMA or implants, the NPs of Ag, Zn, and TiO_2 enhanced both antimicrobial and mechanical properties [16, 17, 19, 20, 24, 25, 38–41, 44, 49, 51–56]. In orthodontic brackets, adhesives, GIC, dentifrices, varnishes, and base plates they were mainly applied as antimicrobial agents [16–20, 24, 26, 28–30, 32–35, 38–40, 51, 54, 59, 60]. In some studies dual metal NPs, like TiO_2 with AgNPs and UV irradiation were used to improve the antimicrobial effect [51].

The antimicrobial efficacy of AgNPs is mainly related to their interaction with the peptidoglycan cell walls of bacteria with resultant release of lipopolysaccharides and membrane proteins [81]. Further, their accumulation in the cell membrane increases the membrane permeability causing cell death. This phenomena was specifically useful for killing the

microorganisms present in the biofilms. Further, their interactions with the exposed sulfhydryl groups in bacterial proteins prevented DNA replication. They even produced ROS that damaged the bacterial cell membranes [82]. An added benefit of AgNPs was reduced incidence of antimicrobial resistance [83].

In the composite resins, the AgNPs were incorporated in the polymer matrix. The Ag ions slowly oxidized to Ag_2O in aerobic conditions. Their release rate was augmented by the acidic environment created by the adhered bacteria [30, 84]. Therefore, these modified composites acted as "smart surface" materials, whereby the concentration of Ag ions was controlled by the bacteria's pathogenic action [30, 84]. They reduced the CFU's of *Streptococcus mutans* (*S. mutans*) without affecting the dentin shear bond strength [16]. When combined with the NPs of amorphous calcium phosphate (NACP), they reduced biofilm formation, increased the release of calcium and phosphate ions, inhibited caries and promoted remineralization of enamel [17, 19, 24]. Likewise, the NPs of ZnO (1%) in composite resins also produced strong bactericidal effect against *S. mutans* and Lactobacilli [20]. In the GICs, the Ag ions (0.5 w/w%) added to the PAA liquid inhibited the growth of *Escherichia coli* (E coli) and *S. mutans* [30, 56]. At 5 w/w% concentration in PMMA, the AgNPs reduced adhesion and biofilm formation by *Candida albicans* (*C. albicans*) [38, 40]. Likewise, alongwith Ca $(OH)_2$ intracanal medicaments, they helped in eliminating the *Enterococcus faecalis* (*E. faecalis*) from the infected root canals [48]. Addition of nano Ag (1% or 10%) to calcium glycerophosphate or to a colloidal solution of chitosan and fluoride in dentifrices, reduced the levels of ATCC strains of *C. albicans* and acid production by *S. mutans* [59, 60]. A combination of ZnO and AgNPs in endodontic sealers effectively controlled the *E. faecalis* proliferation in root canal space [18]. A coating of Ag, TiO_2, and ZnO NPs on the dental implant surfaces prevented biofilm formation by the initial colonizers like *C. albicans*, *Streptococcus sanguis* (*S. sanguis*) and *Actinomyces naeslundii* (*A. naeslundii*) [51, 52, 54–56]. The antimicrobial effect of AgNPs was also demonstrated in randomized controlled clinical trials included in this review [32–35].

The CuO NPs in orthodontic adhesives were bactericidal against the *S. mutans* [7, 58]. Like AgNPs, their bactericidal effect was also related to the production of ROS [85]. The TiO_2 NPs were effective against the *S. mutans*, *S. sanguis*, *A. naeslundii*, *Lactobacillus acidophilus* (*L. acidophilus*), *Candida scotti* (*C. scotti*), and *C albicans* [23, 27, 41, 44, 49, 52, 56]. They were deposited in situ on the denture base resulting in a smoother hydrophilic surface with increased surface wettability [49]. This inhibited the initial attachment of *Candida* on the denture base.

The ZnO NPs incorporated in the dental implants showed bactericidal effect against *Streptococcus*, *Staphylococcus*, and anaerobes [55, 56]. It was suggested that the ZnO NPs selectively targeted *Staphylococcus aureus* (*S. aureus*), and their small particle size increased the penetration into the dentinal tubules [86]. This facilitated elimination of *E. faecalis* when used in combination with chlorhexidine as an intracanal medicament [22]. Their coating on orthodontic brackets reduced the levels of *S. mutans* to zero [7]. This was also evident when a combination of CuO and ZnO was incorporated in orthodontic adhesives and brackets [7, 58].

The antimicrobial effect of various nanometals was determined with the help of colony forming units (CFUs) and minimal inhibitory concentrations (MIC). The MIC of AgNPs against *E. coli*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *S. aureus* were 0.49, 0.975, and 1.95 ppm respectively [19]. Their minimum bactericidal concentration (MBC) and MIC ratio was ≤ 4 which indicated that AgNPs were strongly bactericidal against these organisms [19]. Furthermore, the MIC against the *C. albicans* and *S. mutans* was influenced by the type of reducing agent used for preparing the Ag ions, as it affected their concentration [59]. In dentifrices, a 200 ppm concentration of AgNPs was inhibitory for the *S. mutans* [60].

ii. Mechanical properties

The nano metal particles like Ag, ZnO, TiO_2, and ZrO_2 improved the compressive, flexural and microhardness of various dental materials at a relatively low filler level [6, 16, 23, 24, 27, 28, 30, 36, 39, 42, 43, 45–50, 58]. This was related to their nano scale size that increased their surface area. However, incorporation of 5 wt % of AgNPs to PMMA reduced its tensile strength, owing to reduced number of particles per unit area of the matrix and void formation from the entrapped air and moisture [39]. The heterogenous dispersion and agglomeration of the particles produced stress concentration centers that prevented chemical bond formation between the AgNPs and PMMA [39, 87]. Conversely, the AgNPs increased the compressive strength of GIC by 32% when they were homogeneously distributed in the matrix as increased crosslinking between the polymer chains prevented crack propagation [30]. Like AgNPs, the TiO_2 NPs also improved the flexural and compressive strengths as well as micro hardness of the GIC [23, 27].

Some studies have demonstrated that incorporation of AgNPs to nano ZnO based endodontic sealers, increased microleakage [18, 21]. This was attributed to the larger particle size of ZnO:Ag composites which could not diffuse into the root bone junction [18, 21]. The microleakage was minimum with ZnO nano-powders calcined at 500 °C [21]. Alternatively, the ZnO NPs increased the microshear bond strength and reduced microleakage of composite resins [25]. They reduced the dentinal fluid flow, increased the complex modulus values at intertubular and peritubular dentin, fastened

the active dentin remodeling and tubular occlusion which reduced the dentinal hypersensitivity [28, 61].

The nano Zr significantly increased the flexural strength and surface hardness of the PMMA [42, 43, 45- 48, 50]. This was attributed to the phenomena of "dispersion strengthening" whereby the small, tough, and crystalline Zr NPs, homogeneously distributed in the PMMA matrix, prevented the crack propagation [45, 88]. However, a study showed that a 5 wt% concentration of these NPs reduced the flexural strength due to agglomeration of the untreated nanofillers [47]. Conversely, a 7.5 wt% concentration of nano-ZrO_2 when added to the unreinforced resin, increased its flexural strength [43]. It was suggested that the silanization process and the joint's surface design, played an important role in improving the properties of PMMA [43]. The transformation of ZrO_2 from the tetragonal to monoclinic phase, absorbed the energy of crack propagation resulting in "transformation toughening" [43]. It expanded the ZrO_2 crystals which placed the crack under compressive stress and arrested its propagation. They even increased the transverse strength of autopolymerized resin. This was related to increased interfacial shear bond between the NPs and the polymeric chains [42, 89]. The maximal transverse strength was recorded with 5 wt% of nano Zr. Conversely, another study reported reduction in transverse strength when various ratios (5, 10, and 20%) of nano-ZrO_2 were added to the heat-cured PMMA [47]. It was related to a non-homogenous distribution of the NPs and water sorption in the microcracks within the PMMA matrix. Besides, combination of glass fibers (GFs) with nano ZrO_2 (2.5% nano-ZrO_2 + 2.5% GFs) increased the flexural strength of PMMA by 45% and impact strength by 51% [50]. An inverse relationship was seen between the concentration of ZrO_2 NPs/GFs and the flexural strength. However, addition of ZrO_2 NPs to PMMA hindered its translucency due to differences in the optical properties and distribution within the resin matrix [48]. As the ZrO_2 NPs were crystalline (high opacity) and formed clusters, the absorbed light was unable to pass resulting in decreased translucency. The difference between the refractive indices of the fillers and matrix affected the refraction and reflection of light at the filler/matrix interface. These effects were inversely proportional to the concentration of ZrO_2 NPs.

Besides the PMMA, the ZrO_2 NPs improved the compressive strength and radio-opacity of the Portland/MTA cement [36, 37]. The MTA consists of calcium silicate and a radio pacifying agent, the bismuth oxide (Bi_2O_3) in 4:1 ratio [36]. The Bi_2O_3 confers high radio-opacity to Portland cement but interferes with its hydration mechanism [36, 90]. It causes precipitation of $Ca(OH)_2$, alters the microstructure of the cement, and increases its porosity and solubility [36]. It is mildly cytotoxic as it interferes with human dental pulp cell growth [36, 91]. The ZrO_2 NPs (1:4 ratio) were used as an alternative to Bi_2O_3 in MTA or Portland cement [36, 37]. It provided adequate radiopacity along with the release of calcium ions and alkaline pH without affecting the hydration reaction [36, 37]. Improved mechanical properties were also seen in yittria reinforced Zr sintered to ceramics [46].

Besides, the size of NPs, the technique of their deposition may influence the mechanical properties [49]. For instance, deposition of a nano thickness film of TiO_2 on the denture base by ALD technique, improved its wear resistance and decreased the wetting angle to 5° [49].

The TiO_2 NPs added at 3 and 5 w/w% concentrations to GIC, significantly enhanced its fracture toughness, compressive and flexural strengths and hardness [23]. A dually modified GIC with chitosan in the liquid phase and TiO_2 NPs in the powder phase showed similar effects [27]. However, a previous study reported that incorporation of 7% (w/w) of TiO_2 NPs compromised the mechanical properties and adhesion of GIC [23, 92].

iii. Bone regeneration

The nanometals may stimulate osseointegration, i.e., formation of a direct connection between living bone and the dental implants [31]. For instance, a study utilizing AuNP-calcium phosphate cement (CPC) scaffold suggested that AuNPs induced osteogenic differentiation of human dental pulp stem cells (hDPSCs) [31]. They improved the wetting, protein adsorption, cell attachment, and spreading properties of CPCs. The AuNP-CPC scaffold enhanced the cell functions and inhibited osteoclast formation. It easily conjugated with Ti and promoted the osteogenic differentiation of other cells like human adipose derived stem cells [57].

Likewise, the sol-gel–derived nanoporous TiO_2 coatings enhanced the soft-tissue attachment around implants in both animal and human models [52]. A study showed that the TiO_2 deposited by a fast electrochemical anodization treatment produced nano-tubes on the Ti surfaces which enhanced the bone growth, protein adsorption, and cell adhesion [53]. Some studies incorporated AgNPs into these nanotubes which promoted osseointegration [51, 55, 56].

Toxicity Related to Nanometals Used in Dentistry

Although nanometals provide numerous benefits, very little is known about their toxic effects on humans, specifically when incorporated in the dental materials. Evidence from short-term in vitro studies shows that the nano dental materials are non-cytotoxic [62–64, 66, 67]. However, these results cannot be generalized. As the dental materials remain functional in the oral cavity for a longer duration, there is a high probability that the NPs from these materials may leach out into the saliva and produce systemic effects [15]. They undergo biodegradation in the oral environment which includes both destruction and dissolution in saliva as well as chemical/physical destruction, wear, and erosion caused by food, chewing, and bacterial activity [93].

Therefore, the material reactivity in the oral cavity is mainly governed by the thermo-dynamic principles and electrochemical reaction kinetics. Subsequently, when an alloy is placed in the oral cavity, the alloy-saliva system is driven towards a state of thermo-dynamic equilibrium. At this stage, the alloy may remain stable in its elemental form or oxidize into its ionic form (corrosion). The uncharged elements inside the alloy may lose electrons and become positively charged ions which are released into the saliva. They may affect the surrounding tissues or enter the systemic circulation [93]. The same mechanism may be applied to the nano metals used in dental restorations. Therefore, it is imperative to evaluate their long-term toxic effects. Since there were no studies related to this aspect, the following section would describe the factors affecting and mechanism of toxicity induced by nano metal particles. Further the studies evaluating their toxic effects when included in dental materials would be discussed [62–67].

Mechanism of Toxicity from Nanometal Particles

The toxicity depends on different parameters like size, surface area, surface characteristics, stability, and routes of exposure resulting in cytotoxicity, genotoxicity, increased inflammation and reticuloendothelial system (RES) toxicity (Fig. 2) [94]. Their adverse effects on different organ systems have been listed in Table 3 [95–111]. These factors were detailed in an earlier study [94].

a) Size and surface area of nano metal particles

The size of nanometal particles mediates the cell responses, including uptake, cyto-toxicity, ability to penetrate the biological barriers, and immunological responses [112]. As the size decreases, the surface area to volume ratio increases which subsequently increases their reactivity. For instance, the ROS generation and degradation of AgNPs into ions is dependent on their size [113]. It has been reported that a reduction in particle size from 30 to 3 nm increases the number of surface particles from 5 to 50% which subsequently increases their chemical reactivity [94, 114]. These surface atoms affect the cell organelles like mitochondria, lysosomes, nucleus, and genetic material resulting in cytotoxicity and genotoxicity.

Studies have shown that NPs of metals like Ag are easily internalized due to their small size and induce changes in the cell shape and viability [96]. Their active surface stimulates generation of ROS and hydroxyl radicals from lysosomes, leading to increased oxidative stress [113, 115]. The lysosomes become swollen and their membranes rupture due to lipid peroxidation [113, 116]. Eventually, the cathepsins are released into the cytoplasm which activates the lysosome-mediated apoptosis [116]. It has been shown that the AgNPs and Ag ions have preference for the thiol groups [113]. Therefore, the molecules with thiols in the cytoplasm, cell membrane, and inner membrane of mitochondrion, serve as their targets [113, 117]. As a result of lipid peroxidation, the membrane permeability increases and the cytoplasmic contents are leaked out, resulting in cell necrosis. The damage to mitochondrial membrane hinders electron transfer and adenosine triphosphate production which further triggers oxidative stress, and mitochondrion-dependent apoptosis [113, 116, 118]. The nanometer particle size also enables the AgNPs to translocate into the nucleus with the help of nuclear pore complexes [113]. Inside the nucleus they interact with the DNA leading to DNA damage through the direct or indirect mechanisms. The direct DNA damage involves localization of the NP in the nucleus causing mutations while the indirect genotoxicity occurs due to oxidative stress [94, 119]. The latter is related to chronic inflammation caused by activation/recruitment of immune cells, such as macrophages and/or neutrophils by the NPs. The nano metal particles of Ag, Au, and metal oxides like TiO_2 and ZnO have been reported to cause DNA damage [94, 119, 120].

Although the nano metal particles and their oxides are believed to inhibit the production of pro-inflammatory cytokines, their interaction with the immune system cells (leukocytes, neutrophils, monocytes, platelets, dendritic cells and macrophages) may result in pro-inflammatory effects [94]. The NPs like those of Ag may enhance the release of cytokines like interleukin (IL)-1β by inducing inflammasome formation and caspase-1 activation [116]. They were reported to be cytotoxic to human blood monocytes. Stimulation of cell signaling pathways (e.g., nuclear factor kappa–B (NF-κB), mitogen activated protein (MAP)-kinase) accentuates the release of other pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α) [78, 94] (Fig. 2). The NPs of Au, Ti, Cu, and Zn have also been shown to produce similar effects through activation of these pathways [120–122]. The transition metals in metallic NPs may further enhance these processes by inducing Fenton's and Heiber-Weiss reaction [123, 124]. This phenomena has been reported with the AgNPs. Its apoptotic effects have been attributed to activation of c-Jun N-terminal kinase (JNK) pathway [125]. The ZnO NPs damage the mitochondria as toxic concentrations of Zn ions destabilize the lysosomes. Their internalization or interaction with the cell surface induces toxicity by similar mechanisms [94, 126].

The RES clears the NPs by directing them towards the liver and spleen [127]. They are sequestered or filtered by the kidney. It has been noted that less than 5% of NPs reach the diseased site and the rest are cleared by the liver, spleen, and kidneys [128]. In general, the NPs of about 10 nm size are rapidly filtered out by the kidneys while those larger than 200 nm are cleared by the spleen [129]. The nanometal particles used in the dental materials fall in this range and may have a role in RES toxicity, which needs further verification.

Table 3 Toxic effects of various nanometals and their compounds on body organs

Organ	Nano metal/ oxide	Toxic effects produced
Brain [96–99]	Ag	The embryonic neural stem cells (NSCs) from human and rat fetuses showed: • Reduced mitochondrial viability • Increased LDH release • Up-regulated Bax protein expression • Increased number of TUNEL-positively stained cells • Increased ROS Altered cognition in BALB/C mice Mitochondrial damage Acute calcium response Changes in astrocyte morphology
	TiO_2	• Increased oxidative stress • Increased inflammatory responses • Apoptosis • Genotoxicity • Impaired cellular components
	Au	• Astrogliosis • Increased seizure activity • Cognition defects
	Cu	• Crosses the blood-brain barrier • Neuromuscular toxicity
Lung [100]	ZnO Ag Cu/CuO TiO_2	• Increased oxidative stress • Cellular apoptosis • DNA damage
Heart [95, 101]	Ag	• Increased cardiocyte deformity • Increased lipid peroxidation • Decreased levels of GSH, SOD and CAT
Skin [95, 102, 103]	Ag	• Increased oxidative stress • Cellular apoptosis
	TiO_2	• Cellular apoptosis
Liver [95, 104–106]	Ag	• Increased oxidative stress • Increased release of inflammatory mediators
	ZnO	• Increased oxidative stress • Cellular apoptosis
	TiO_2	• Increased oxidative stress • Cellular apoptosis
Kidney [95, 107–110]	Au	• Increased levels of urea, ALT, creatinine
	ZnO	• Increased levels of urea, ALT, creatinine, reduced blood indices
	CuO	• Increased ROS, DNA fragmentation
	TiO_2	• DNA damage
Spleen [95]	Ag	• Inhibits mitochondrial ATP-ase

b) Surface characteristics

The surface of NPs is one of the important factors determining their toxicity potential as it influences their cellular uptake. The cationic NPs are more reactive when compared with the anionic ones and can be easily taken up by the cells [94, 130, 131]. This is mainly related to the electrostatic attraction between the negatively charged cell membrane glycoproteins and positively charged NPs [115]. They are also more strongly bound to the negatively charged DNA and damage it. Subsequently, the G0/G1 phase of the cell cycle is prolonged [132]. Studies have shown that positively charged AuNPs were easily adsorbed on the cells and were more toxic when compared with their negatively charged counterparts [133].

The positively charged metal NPs have enhanced opsonization potential, i.e., they promote adsorption of proteins including antibodies and complement components, from blood and biological fluids like saliva on their surfaces [132, 134]. These adsorbed proteins form "protein coronas" which affect the surface properties of the NPs [132]. For example, they may alter the surface charge, aggregation characteristics, or size of the NPs [132]. The conformational changes in the proteins may alter or inhibit their functional activities as well. They may either lose their enzymatic action or disturb the biological processes resulting in diseases [132]. Certain techniques have been developed for changing the surface charge of the NPs in order to improve their therapeutic efficacy and reduce toxicity. For example, the NP surfaces and their charges could be modified by grafting differently charged polymers like polyethylene glycol or folic acid to improve their intracellular uptake [135]. The biocompatibility of TiO_2 NPs was improved through incorporation of functional NH_2 or SH groups [136].

As the nanometal particles used in dental materials are cationic in nature, they may easily penetrate the cells and induce toxicity. They may either stimulate or suppress the immunogenic responses and toxicity in vivo [94, 137].

The shape of NPs also affects their cellular uptake. For instance, rod-shaped AuNPs were readily taken up by the dendritic cells than the spherical- or cubic-shaped particles. This was related to the larger surface volume of rod shaped particles, which may then have increased toxic effects [138].

c) Stability of NPs and presence of impurities

The chemically stable NPs are less toxic when compared to the unstable ones. Moreover, NPs with impurities may readily undergo aggregation. This increases their toxicity due to excessive generation of ROS and inflammatory mediators [94]. This was reported with AgNPs in animal studies [139].

d) Route of exposure

The exposure route determines the initial interaction of NPs with cells/tissues. The most common routes of exposure include inhalation or direct contact with materials containing NPs [94]. They may reach toxic concentrations in the body

which may affect the brain, liver, spleen, lymph nodes, and other organs [94]. Increased exposure to metal oxide NPs (ZnO, TiO_2, Al_2O_3, or CeO_2) by aerosol reduced the tidal volume and increased the respiratory rate in mice [140]. The NPs of ZnO and TiO_2 may induce nasal irritation. The ZnO NPs may cause significant toxic effect in the airways while TiO_2 may result in DNA-strand break.

Toxicity Studies on Nanometal Particles and Their Oxides in Dental Materials

The dental patients as well as the practitioners may be exposed to NPs of metals and their oxides either through accidental or incidental ingestion of the dental materials [141]. Although the dental materials for permanent restorations are investigated for their stability and biocompatibility in oral environment, toxic compounds may be generated through material degradation, or inappropriate application by the clinician [15]. This was reported with the use of dental amalgams and metal alloys used for crown fabrication [142, 143]. However, similar information for dental materials containing nano metal particles is lacking. The NPs generated during treatment may cause systemic toxicity or direct toxicity to the cells/tissue of the oral mucosa. These effects have been evaluated in various in vitro and animal studies that focused on exposure to TiO_2, ZrO_2, and Ag NPs [62–67] (Table 2).

The occupational exposure may occur in dental laboratories or clinics whereby NPs of metals may be released during the manipulation of the materials [141]. This includes mixing of materials in paste form or milling of the set materials. For instance, peak concentrations of these NP in the aerosol were observed when the dentist was finishing or polishing the set composite restorations on the front teeth without water coolant [141, 144, 145]. It was found that the aerosol mainly contained the nano-sized particles with concentrations above 10^6 particles/cm^3, in the breathing zone of both patient and the dentist [141, 145]. The NPs of metals are rarely released from the set materials in the patient's oral cavity. However, they may be generated through wear process and swallowed. These NPs apparently reach the intestine from where they may enter into the lymphatic system [141]. The wear rates have been reported to be least for ceramic restorations followed by the composites and GICs [141, 146].

Previous research work has demonstrated that NPs of TiO_2 may be absorbed across the lungs and gastrointestinal tract [147]. The Ti NPs may be released from the dental implants into the surrounding periodontal tissues or newly regenerated bone [141, 148–150]. A postmortem study showed that highest concentration of Ti NPs generated during or after the insertion of implants was in human mandibular bone (37,700 μg/kg of bone weight at a distance of 556–1587 μm from the implants) [141, 151]. Their concentrations were inversely proportional to the distance from the implants. The sizes of particles ranged between 0.5 and 40 μm in human jaw bone marrow tissues, at distances of 60–700 μm from dental implants [141, 151]. The AgNPs release rate has been found to be 550 μg/l after 168 h [152]. There is also a risk of exposure from environmental contamination due to improper disposal of dental materials containing nanometal particles.

In vivo studies on rodents revealed increased accumulation of nano metals from dental materials in the internal organs which could result in organ pathology. For instance, single oral gavage of TiO_2 NPs (25 or 80 nm) caused pathological changes in the liver and kidney of mice; chronic ingestion of colloidal silver solution caused argyria in humans [153, 154]. A recent review suggested that NPs of metals like Au, Ag, and Ti from dental materials could cross the blood-brain barrier or translocate through sensory nerves resulting in neurotoxicity [155].

As the oral epithelium is mostly non-keratinized stratified squamous epithelium, with the exception of gingiva, hard palate and dorsal surface of the tongue, there is a plausibility for direct contact of NPs with the cells and tissues of the oral cavity [15]. They may induce hypersensitivity reactions or inflammation in a vulnerable patient. The Ag, TiO_2, ZnO, and Au NPs commonly used in dental materials may slowly dissolve into more toxic ionic forms. However, the studies have reported that these metals were not cytotoxic to the surrounding cells. For instance, a novel AgNPs endodontic irrigant was not cytotoxic to human periodontal ligament stem cells (hPDLSCs) and the mouse fibroblasts over a 48-hperiod [64]. Similarly, Ag NPs incorporated in MTA did not cause any reaction in the rat connective tissue [65]. The GICs containing Zr NPs and microparticles were reported to be non-genotoxic [67]. Although the TiO_2 NPs, are considered to be non-cytotoxic, moderate cytotoxicity on human gingival fibroblasts was reported when they were incorporated in an orthodontic adhesive (1% w/w) [63, 66]. However, the cell viability percentages were similar to the unmodified adhesive [63]. Other NPs like those of Au in injectable calcium phosphate cement have been demonstrated inside the hDPSCs and postulated to interfere with the cellular behavior [31].

Recommendations to Reduce Toxicity from Dental Materials Containing Nanometal Particles

As the data on possible adverse reactions derived from metal NPs in dental materials or from manipulation of these materials is sparse, more research is required in this direction. Following suggestions may be helpful in preventing exposure to the metal NPs [141]:

1. The safety regulations for all dental materials should be strictly followed by the dental professionals.

2. The amount of dust generated may be reduced through proper carving of the restorations.
3. Barrier techniques like use of mouth masks or face shields may be helpful in reducing the exposure from aerosol released during handling of set materials.
4. High vacuum suctions or evacuators and coolants should be used when grinding and polishing the restorations intraorally.
5. Effective ventilation in treatment areas prevents accumulation of the particles in the localized environment and hence inhalation.
6. Encapsulated powder/liquid systems should be used to avoid exposure during manipulation of materials.
7. Stability of restorations and prostheses like Ti implants is imperative to prevent leaching of NPs during functional movements in oral cavity.
8. The surface charge of metal NPs may be modified with help of charged polymers like poly (lactic-co-glycolic acid) for targeted drug delivery in oral cavity with minimal toxicity [156].
9. The pulmonary toxicity of metal oxide NPs may be reduced with the help of phosphonate surface passivation [157].

Conclusion

The nanometals and their oxides have numerous applications in dentistry owing to their favorable antimicrobial, mechanical and regenerative properties. However, their potential benefits are often accompanied with the risk for toxicity owing to their nanoscale size and reactivity. Although in vitro studies suggest that these materials are noncytotoxic, there is a dearth of evidence on this aspect. As the current research lacks a unifying protocol for the toxicological profiling of NPs of metals used in dental materials, there is a need for well-designed clinical trials which would evaluate their plausible adverse oro-systemic effects in humans.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Slokar L, Pranjić J, Carek A (2017) Metallic materials for use in dentistry. The holistic approach to environment 7:39–58
2. Gettleman L (1991) Noble alloys in dentistry. Curr Opin Dent 1: 218–221
3. Schmalz G, Hickel R, van Landuyt KL, Reichl FX (2017) Nanoparticles in dentistry. Dent Mater 33:1298–1314. https://doi.org/10.1016/j.dental.2017.08.193
4. Govindankutty D (2015) Applications of nanotechnology in orthodontics and its future. Inter J App Dent Sci 1:166–171
5. Al-Nafori MK, Elshal MG, Refai WM (2017) The effect of incorporating gold and silver nanoparticles in orthodontic adhesive system on bond strength of orthodontic bracket. EC Dental Science 11:119–131
6. Felemban NH, Ebrahim MI (2017) The influence of adding modified zirconium oxide-titanium dioxide nano-particles on mechanical properties of orthodontic adhesive: an in vitro study. BMC Oral Health 17:1–8. https://doi.org/10.1186/s12903-017-0332-2
7. Ramazanzadeh B, Jahanbin A, Yaghoubi M, Shahtahmassbi N, Ghazvini K, Shakeri M, Shafaee H (2015) Comparison of antibacterial effects of ZnO and CuO nanoparticles coated brackets against streptococcus mutans. J Dent (Shiraz) 16:200–205
8. Redlich M, Katz A, Rapoport L, Wagner HD, Feldman Y, Tenne R (2008) Improved orthodontic stainless steel wires coated with inorganic fullerene-like nanoparticles of WS(2) impregnated in electroless nickel-phosphorous film. Dent Mater 24:1640–1646. https://doi.org/10.1016/j.dental.2008.03.030
9. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT, Yacaman MJ (2005) The bactericidal effect of silver nanoparticles. Nanotechnology 16:2346–2353. https://doi.org/10.1088/0957-4484/16/10/059
10. Sirelkhatim A, Mahmud S, Seeni A, Kaus NHM, Ann LC, Bakhori SKM, Hasan H, Mohamad D (2015) Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. Nano Lett 7:219–242. https://doi.org/10.1007/s40820-015-0040-x
11. Yildirimer L, Thanh NTK, Loizidou M, Seifalian AM (2011) Toxicology and clinical potential of nanoparticles. NanoToday 6: 585–607. https://doi.org/10.1016/j.nantod.2011.10.001
12. Faria AC, Rodrigues RC, Antunes RP, de Mattos MG, Rosa AL, Ribeiro RF (2009) Effect of temperature variation on the cytotoxicity of cast dental alloys and commercially pure titanium. J Appl Oral Sci 17:421–426. https://doi.org/10.1590/S1678-77572009000500013
13. Chaturvedi TP1, Upadhayay SN (2010) An overview of orthodontic material degradation in oral cavity. Indian J Dent Res 21:275-284.https:// doi: https://doi.org/10.4103/0970-9290.66648.
14. Behzadi S, Serpooshan V, Tao W, Hamaly MA, Alkawareek MY, Dreaden EC, Brown D, Alkilany AM, Farokhzad OC, Mahmoudi M (2017) Cellular uptake of nanoparticles: journey inside the cell. Chem Soc Rev 46:4218–4244. https://doi.org/10.1039/c6cs00636a
15. Besinis A, De Peralta T, Tredwin CJ, Handy RD (2015) Review of nanomaterials in dentistry: interactions with the oral microenvironment, clinical applications, hazards, and benefits. ACS Nano 9: 2255-2289. https:// doi: https://doi.org/10.1021/nn505015e.
16. Cheng L, Zhang K, Weir MD, Liu H, Zhou X, Xu HH (2013) Effects of antibacterial primers with quaternary ammonium and nano-silver on Streptococcus mutans impregnated in human dentin blocks. Dent Mater 29:462–472. https://doi.org/10.1016/j.dental.2013.01.011
17. Zhang K, Cheng L, Imazato S, Antonucci JM, Lin NJ, Lin-Gibson S, Bai Y, Xu HH (2013) Effects of dual antibacterial agents MDPB and nano-silver in primer on microcosm biofilm, cytotoxicity and dentine bond properties. J Dent 41:464–474. https://doi.org/10.1016/j.jdent.2013.02.001
18. Rad MS, Kompany A, Zak AK, Javidi M, Mortazavi SM (2013) Microleakage and antibacterial properties of ZnO and ZnO: Ag nanopowders prepared via a sol–gel method for endodontic sealer application. J Nano Res. https://doi.org/10.1007/s11051-013-1925-6

19. Dugal S, Chakraborty S (2014) Application of nanosilver for prevention of recurrent dental caries in patients suffering from xerostomia. Int J Pharm Pharm Sci 6:101–104
20. Kasraei S, Sami L, Hendi S, Alikhani MY, Rezaei-Soufi L, Khamverdi Z (2014) Antibacterial properties of composite resins incorporating silver and zinc oxide nanoparticles on Streptococcus mutans and Lactobacillus. Restor Dent Endod 39: 109–114. https://doi.org/10.5395/rde.2014.39.2.109
21. Javidi M, Zarei M, Naghavi N, Mortazavi M, Nejat AH (2014) Zinc oxide nano-particles as sealer in endodontics and its sealing ability. Contemp Clin Dent 5:20–24. https://doi.org/10.4103/0976-237X.128656
22. Aguiar AS, Guerreiro-Tanomaru JM, Faria G, Leonardo RT, Tanomaru-Filho M (2015) Antimicrobial activity and pH of calcium hydroxide and zinc oxide nanoparticles intracanal medication and association with chlorhexidine. J Contemp Dent Pract 16: 624–629
23. Garcia-Contreras R, Scougall-Vilchis RJ, Contreras-Bulnes R, Sakagami H, Morales-Luckie RA, Nakajima H (2015) Mechanical, antibacterial and bond strength properties of nano-titanium-enriched glass ionomer cement. J Appl Oral Sci 23:321–328. https://doi.org/10.1590/1678-775720140496
24. Cheng L, Zhang K, Zhou CC, Weir MD, Zhou XD, Xu HH (2016) One-year water-ageing of calcium phosphate composite containing nano-silver and quaternary ammonium to inhibit biofilms. Int J Oral Sci 8:172–181. https://doi.org/10.1038/ijos.2016.13
25. Teymoornezhad K, Alaghehmand H, Daryakenari G, Khafri S, Tabari M (2016) Evaluating the microshear bond strength and microleakage of flowable composites containing zinc oxide nano-particles. Electron Physician 8:3289–3295. https://doi.org/10.19082/3289
26. Afkhami F, Pourhashemi SJ, Sadegh M, Salehi Y, Fard MJ (2015) Antibiofilm efficacy of silver nanoparticles as a vehicle for calcium hydroxide medicament against Enterococcus faecalis. J Dent 43:1573–1579. https://doi.org/10.1016/j.jdent.2015.08.012
27. Ibrahim MA, Meera Priyadarshini B, Neo J, Fawzy AS (2017) Characterization of chitosan/TiO_2 nano-powder modified glass-ionomer cement for restorative dental applications. J Esthet Restor Dent 29:146–156. https://doi.org/10.1111/jerd.12282
28. Nozari A, Ajami S, Rafiei A, Niazi E (2017) Impact of nano hydroxyapatite, nano silver fluoride and sodium fluoride varnish on primary teeth enamel remineralization: an in vitro study. J Clin Diagn Res. https://doi.org/10.7860/JCDR/2017/30108.10694
29. Scarpelli BB, Punhagui MF, Hoeppner MG, Almeida RSC, Juliani FA, Guiraldo RD, Berger SB (2017) In vitro evaluation of the remineralizing potential and antimicrobial activity of a cariostatic agent with silver nanoparticles. Braz Dent J 28:738–743. https://doi.org/10.1590/0103-6440201701365
30. Paiva L, Fidalgo TKS, da Costa LP, Maia LC, Balan L, Anselme K, Ploux L, Thiré RMSM (2018) Antibacterial properties and compressive strength of new one-step preparation silver nanoparticles in glass ionomer cements (NanoAg-GIC). J Dent 69:102–109. https://doi.org/10.1016/j.jdent.2017.12.003
31. Xia Y, Chen H, Zhang F, Bao C, Weir MD, Reynolds MA, Ma J, Gu N, Xu HHK (2018) Gold nanoparticles in injectable calcium phosphate cement enhance osteogenic differentiation of human dental pulp stem cells. Nanomedicine 14:35–45. https://doi.org/10.1016/j.nano.2017.08.014
32. Santos VE Jr, Vasconcelos Filho A, Targino AG, Flores MA, Galembeck A, Caldas AF Jr, Rosenblatt A (2014) A new "silver-bullet" to treat caries in children—nano silver fluoride: a randomized clinical trial. J Dent 42:945–951. https://doi.org/10.1016/j.jdent.2014.05.017
33. Ghorbanzadeh R, Pourakbari B, Bahador A (2015) Effects of baseplates of orthodontic appliances with in situ generated silver nanoparticles on cariogenic bacteria: a randomized, double-blind cross-over clinical trial. J Contemp Dent Pract 16:291–298
34. Freire PLL, Albuquerque AJR, Sampaio FC, Galembeck A, Flores MAP, Stamford TCM, Rosenblatt A (2017) AgNPs: the new allies against S mutans biofilm – a pilot clinical trial and microbiological assay. Braz Dent J 28:417–422. https://doi.org/10.1590/0103-6440201600994
35. Tirupathi S, Svsg N, Rajasekhar S, Nuvvula S (2019) Comparative cariostatic efficacy of a novel nano-silver fluoride varnish with 38% silver diamine fluoride varnish a double-blind randomized clinical trial. J Clin Exp Dent. https://doi.org/10.4317/jced.54995
36. Silva GF, Bosso R, Ferino RV, Tanomaru-Filho M, Bernardi MI, Guerreiro-Tanomaru JM, Cerri PS (2014) Microparticulated and nanoparticulated zirconium oxide added to calcium silicate cement: evaluation of physicochemical and biological properties. J Biomed Mater Res A 102:4336–4345. https://doi.org/10.1002/jbm.a.35099
37. Silva GF, Guerreiro-Tanomaru JM, da Fonseca TS, Bernardi MIB, Sasso-Cerri E, Tanomaru-Filho M, Cerri PS (2017) Zirconium oxide and niobium oxide used as radiopacifiers in a calcium silicate-based material stimulate fibroblast proliferation and collagen formation. Int Endod J. https://doi.org/10.1111/iej.12789
38. Suganya S, Ahila SC, Kumar BM, Kumar MV (2014) Evaluation and comparison of anti-Candida effect of heat cure polymethylmethacrylate resin enforced with silver nanoparticles and conventional heat cure resins: an in vitro study. Indian J Dent Res 5:204-207. https:// doi: https://doi.org/10.4103/0970-9290.135923.
39. Ghaffari T, Hamedi-Rad F (2015) Effect of silver nano-particles on tensile strength of acrylic resins. J Dent Res Dent Clin Dent Prospects 9:40-43. https:// doi:https://doi.org/10.15171/joddd.2015.008.
40. Li Z, Sun J, Lan J, Qi Q (2016) Effect of a denture base acrylic resin containing silver nanoparticles on Candida albicans adhesion and biofilm formation. Gerodontology 33:209–216. https://doi.org/10.1111/ger.12142
41. Sodagar A, Khalil S, Kassaee MZ, Shahroudi AS, Pourakbari B, Bahador A (2016) Antimicrobial properties of poly (methyl methacrylate) acrylic resins incorporated with silicon dioxide and titanium dioxide nanoparticles on cariogenic bacteria. J Orthod Sci 5: 7–13. https://doi.org/10.4103/2278-0203.176652
42. Gad M, ArRejaie AS, Abdel-Halim MS, Rahoma A (2016) The reinforcement effect of nano-zirconia on the transverse strength of repaired acrylic denture base. Int J Dent. https://doi.org/10.1155/2016/7094056
43. Gad MM, Rahoma A, Al-Thobity AM, ArRejaie AS (2016) Influence of incorporation of ZrO2 nanoparticles on the repair strength of polymethyl methacrylate denture bases. Int J Nanomedicine 11:5633–5643. https://doi.org/10.2147/IJN.S120054
44. Totu EE, Nechifor AC, Nechifor G, Aboul-Enein HY, Cristache CM (2017) Poly (methyl methacrylate) with TiO_2 nanoparticles inclusion for stereolitographic complete denture manufacturing - the fututre in dental care for elderly edentulous patients? J Dent 59: 68–77. https://doi.org/10.1016/j.jdent.2017.02.012
45. Alhavaz A, Rezaei Dastjerdi M, Ghasemi A, Ghasemi A, Alizadeh Sahraei A (2017) Effect of untreated zirconium oxide nanofiller on the flexural strength and surface hardness of autopolymerized interim fixed restoration resins. J Esthet Restor Dent 29:264–269. https://doi.org/10.1111/jerd.12300
46. Elias CN, dos Santos HES, Garbossa M, dos Santos C (2017) Mechanical properties of zirconia Y-TZP core veneered for dentistry applications. J Ceram Sci Technol 8:525–530. https://doi.org/10.4416/JCST2017-00032

47. Ergun G, Sahin Z, Ataol AS (2018) The effects of adding various ratios of zirconium oxide nanoparticles to poly (methyl methacrylate) on physical and mechanical properties. J Oral Sci 60:304–315. https://doi.org/10.2334/josnusd.17-0206
48. Gad MM, Abualsaud R, Rahoma A, Al-Thobity AM, Al-Abidi KS, Akhtar S (2018) Effect of zirconium oxide nanoparticles addition on the optical and tensile properties of polymethyl methacrylate denture base material. Int J Nanomedicine 13:283–292. https://doi.org/10.2147/IJN.S152571
49. Darwish G, Huang S, Knoernschild K, Sukotjo C, Campbell S, Bishal AK, Barão VA, Wu CD, Taukodis CG, Yang B (2019) Improving polymethyl methacrylate resin using a novel titanium dioxide coating. J Prosthodont. https://doi.org/10.1111/jopr.13032
50. Gad MM, Al-Thobity AM, Rahoma A, Abualsaud R, Al-Harbi FA, Akhtar S (2019) Reinforcement of PMMA denture base material with a mixture of ZrO_2 nanoparticles and glass fibers. Int J Dent. https://doi.org/10.1155/2019/2489393
51. Zhao L, Wang H, Huo K, Cui L, Zhang W, Ni H, Zhang Y, Wu Z, Chu PK (2011) Antibacterial nano-structured titania coating incorporated with silver nanoparticles. Biomaterials 32:5706–5716. https://doi.org/10.1016/j.biomaterials.2011.04.040
52. Fröjd V, Linderbäck P, Wennerberg A, Chávez de Paz L, Svensäter G, Davies JR (2011) Effect of nanoporous TiO_2 coating and anodized Ca2+ modification of titanium surfaces on early microbial biofilm formation. BMC Oral Health 11:1–9. https://doi.org/10.1186/1472-6831-11-8
53. Huang HH, Chen JY, Lin MC, Wang YT, Lee TL, Chen LK (2012) Blood responses to titanium surface with TiO2 nanomesh structure. Clin Oral Implants Res 23:379–383. https://doi.org/10.1111/j.1600-0501.2010.02152.x
54. Matsubara VH, Igai F, Tamaki R, Tortamano Neto P, Nakamae AE, Mori M (2015) Use of silver nanoparticles reduces internal contamination of external hexagon implants by Candida albicans. Braz Dent J 26:458–462. https://doi.org/10.1590/0103-644020130087
55. Abdulkareem EH, Memarzadeh K, Allaker RP, Huang J, Pratten J, Spratt D (2015) Anti-biofilm activity of zinc oxide and hydroxyapatite nanoparticles as dental implant coating materials. J Dent 43:1462–1469. https://doi.org/10.1016/j.jdent.2015.10.010
56. Memarzadeh K, Sharili AS, Huang J, Rawlinson SC, Allaker RP (2015) Nanoparticulate zinc oxide as a coating material for orthopedic and dental implants. J Biomed Mater Res A 103:981–989. https://doi.org/10.1002/jbm.a.35241
57. Heo DN, Ko WK, Lee HR, Lee SJ, Lee D, Um SH, Lee JH, Woo YH, Zhang LG, Lee DW, Kwon IK (2016) Titanium dental implants surface-immobilized with gold nanoparticles as osteoinductive agents for rapid osseointegration. J Colloid Interface Sci 469:129–137. https://doi.org/10.1016/j.jcis.2016.02.022
58. Toodehzaeim MH, Zandi H, Meshkani H, Hosseinzadeh Firouzabadi A (2018) The effect of CuO nanoparticles on antimicrobial effects and shear bond strength of orthodontic adhesives. J Dent (Shiraz) 19:1–5
59. Fernandes GL, Delbem ACB, do Amaral JG, Gorup LF, Fernandes RA, de Souza Neto FN, JAS S, Monteiro DR, AMA H, Camargo ER, Barbosa DB (2018) Nanosynthesis of silver-calcium glycerophosphate: promising association against oral pathogens. Antibiotics (Basel). https://doi.org/10.3390/antibiotics7030052
60. Teixeira JA, Silva AVCE, Dos Santos Júnior VE, de Melo Júnior PC, Arnaud M, Lima MG, Flores MAP, Stamford TCM, Dias Pereira JR, Ribeiro Targino AG, Galembeck A, Rosenblatt A (2018) Effects of a new nano-silver fluoride-containing dentifrice on demineralization of enamel and Streptococcus mutans adhesion and acidogenicity. Int J Dent. https://doi.org/10.1155/2018/1351925
61. Toledano-Osorio M, Osorio E, Aguilera FS, Luis Medina-Castillo A, Toledano M, Osorio R (2018) Improved reactive nanoparticles to treat dentin hypersensitivity. Acta Biomater 72:371–380. https://doi.org/10.1016/j.actbio.2018.03.033
62. Heravi F, Ramezani M, Poosti M, Hosseini M, Shajiei A, Ahrari F (2013) In vitro cytotoxicity assessment of an orthodontic composite containing titanium-dioxide nano-particles. J Dent Res Dent Clin Dent Prospects 7:192–198. https://doi.org/10.5681/joddd.2013.031
63. Garcia-Contreras R, Scougall-Vilchis RJ, Contreras-Bulnes R, Kanda Y, Nakajima H, Sakagami H (2014) Effects of TiO2 nano glass ionomer cements against normal and cancer oral cells. In Vivo 28:895–907
64. Chan EL, Zhang C, Cheung GS (2015) Cytotoxicity of a novel nano-silver particle endodontic irrigant. Clin Cosmet Investig Dent 7:65–74. https://doi.org/10.2147/CCIDE.S68874
65. Zand V, Lotfi M, Aghbali A, Mesgariabbasi M, Janani M, Mokhtari H, Tehranchi P, Pakdel SM (2016) Tissue reaction and biocompatibility of implanted mineral trioxide aggregate with silver nanoparticles in a rat model. Iran Endod J 11:13–16. https://doi.org/10.7508/iej.2016.01.003
66. Akay C, Cevik P, Karakis D, Sevim H (2018) In vitro cytotoxicity of maxillofacial silicone elastomers: effect of nano-particles. J Prosthodont 27:584–587. https://doi.org/10.1111/jopr.12533
67. Laiteerapong A, Reichl FX, Hickel R, Högg C (2019) Effect of eluates from zirconia-modified glass ionomer cements on DNA double-stranded breaks in human gingival fibroblast cells. Dent Mater 35:444–449. https://doi.org/10.1016/j.dental.2019.01.004
68. Chan KHS, Mai Y, Kim H, Tong KCT, Ng D, JCM H (2010) Review: resin composite filling. Materials 3:1228–1243. https://doi.org/10.3390/ma3021228
69. Zhang N, Melo MAS, Weir MD, Reynolds MA, Bai Y, Xu HHK (2016) Do dental resin composites accumulate more oral biofilms and plaque than amalgam and glass ionomer materials? Materials. https://doi.org/10.3390/ma9110888
70. Nair PN, Henry S, Cano V, Vera J (2005) Microbial status of apical root canal system of human mandibular first molars with primary apical periodontitis after "one-visit" endodontic treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99:231–252. https://doi.org/10.1016/j.tripleo.2004.10.005
71. Verran J, Maryan CJ (1997) Retention of Candida albicans on acrylic resin and silicone of different surface topography. J Prosthet Dent 77:535–539
72. Neppelenbroek KH (2015) The importance of daily removal of the denture biofilm for oral and systemic diseases prevention. J Appl Oral Sci 23:547–548. https://doi.org/10.1590/1678-77572015ed006
73. Gowd MS, Shankar T, Ranjan R, Singh A (2017) Prosthetic consideration in implant-supported prosthesis: a review of literature. J Int Soc Prev Community Dent. https://doi.org/10.4103/jispcd.JISPCD_149_17
74. Oshida Y, Tuna EB, Aktören O, Gençay K (2010) Dental implant systems. Int J Mol Sci 11:1580–1678. https://doi.org/10.3390/ijms11041580
75. Mackevica A, Olsson ME, Hansen SF (2017) The release of silver nanoparticles from commercial toothbrushes. J Hazard Mater 322(Pt A):270–275. https://doi.org/10.1016/j.jhazmat.2016.03.067
76. AlKahtani RN (2018) The implications and applications of nanotechnology in dentistry: a review. Saudi Dent J 30:107–116. https://doi.org/10.1016/j.sdentj.2018.01.002
77. Singh J, Dutta T, Kim KH, Rawat M, Samddar P, Kumar P (2018) 'Green' synthesis of metals and their oxide their oxide nanoparticles: applications for environmental remediation. J Nanobiotechnology 16:1–24. https://doi.org/10.1186/s12951-018-0408-4

78. Nel A, Xia T, Mädler L, Li N (2006) Toxic potential of materials at the nanolevel. Science 311:622–627. https://doi.org/10.1126/science.1114397
79. Roduner E (2006) Size matters: why nanomaterials are different. Chem Soc Rev 35:583–592. https:// doi:https://doi.org/10.1039/b502142c.
80. Buffat P, Borel JP (1976) Size effect on the melting temperature of gold particles. Phys Rev A 13:2287–2298. https://doi.org/10.1103/PhysRevA.13.2287
81. Raza MA, Kanwal Z, Rauf A, Sabri AN, Riaz S, Naseem S (2016) Size and shape dependent antibacterial studies of silver nanoparticles synthesized by wet chemical routes. Nanomaterials (Basel). https://doi.org/10.3390/nano6040074
82. Dakal TC, Kumar A, Majumdar RS, Yadav V (2016) Mechanistic basis of antimicrobial actions of silver nanoparticles. Front Microbiol. https://doi.org/10.3389/fmicb.2016.01831
83. Huh AJ, Kwon YJ (2011) "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J Control Release 156:128–145. https://doi.org/10.1016/j.jconrel.2011.07.002
84. Hernández-Sierra JF, Galicia-Cruz O, Angélica SA, Ruiz F, Pierdant-Pérez M, Pozos-Guillén AJ (2011) In vitro cytotoxicity of silver nanoparticles on human periodontal fibroblasts. J Clin Pediatr Dent 36:37–41
85. Applerot G, Lellouche J, Lipovsky A, Nitzan Y, Lubart R, Gedanken A, Banin E (2012) Understanding the antibacterial mechanism of CuO nanoparticles: revealing the route of induced oxidative stress. Small 8:3326–3337. https://doi.org/10.1002/smll.201200772
86. Siddiqi KS, Ur Rahman A, Tajuddin HA (2018) Properties of zinc oxide nanoparticles and their activity against microbes. Nanoscale Res Lett 13:141. https://doi.org/10.1186/s11671-018-2532-3
87. Han Y, Kiat-amnuay S, Powers JM, Zhao Y (2008) Effect of nano-oxide concentration on the mechanical properties of a max-illofacial silicone elastomer. J Prosthet Dent 100:465–473. https://doi.org/10.1016/s0022-3913(08)60266-8
88. Sun L, Gibson RF, Gordaninejad F, Suhr J (2009) Energy absorption capability of nano composites: a review. Compos Sci Technol 69:2392–2409. https://doi.org/10.1016/j.compscitech.2009.06.020
89. Ahmed MA, Ebrahim MI (2014) Effect of zirconium oxide nano-fillers addition on the flexural strength, fracture toughness, and hardness of heat-polymerized acrylic resin. World Journal of Nano Science and Engineering 4:50–57. https://doi.org/10.4236/wjnse.2014.42008
90. Camilleri J (2007) Hydration mechanisms of mineral trioxide aggregate. Int Endod J 40:462–470. https:// doi: https://doi.org/10.1111/j.1365-2591.2007.01248.x
91. Min KS, Kim HI, Park HJ, Pi SH, Hong CU, Kim EC (2007) Human pulp cells response to Portland cement in vitro. J Endod 33:163– 166. https:// doi: https://doi.org/10.1016/j.joen.2006.07.022.
92. Elsaka SE, Hamouda IM, Swain MV (2011) Titanium dioxide nanoparticles addition to a conventional glass-ionomer restorative: influence on physical and antibacterial properties. J Dent 39:589–598. https://doi.org/10.1016/j.jdent.2011.05.006
93. Elshahawy W, Watanabe I (2014) Biocompatibility of dental alloys used in dental fixed prosthodontics. Tanta Dental Journal. https://doi.org/10.1016/j.tdj.2014.07.005.
94. Saifi MA, Khan W, Godugu C (2018) Cytotoxicity of nanomaterials: using nanotoxicology to address the safety concerns of nanoparticles. Pharm Nanotechnol 6:3–16. https://doi.org/10.2174/2211738505666171023152928
95. Ajdary M, Moosavi MA, Rahmati M, Falahati M, Mahboubi M, Mandegary A, Jangjoo S, Mohammadinejad R, Varma RS (2018) Health concerns of various nanoparticles: a review of their in vitro and in vivo toxicity. Nanomaterials (Basel). https://doi.org/10.3390/nano8090634
96. Teleanu DM, Chircov C, Grumezescu AM, Volceanov A, Teleanu RI (2018) Impact of nanoparticles on brain health: an up to date overview. J Clin Med 7:490. https://doi.org/10.3390/jcm7120490
97. Haase A, Rott S, Mantion A, Graf P, Plendl J, Thünemann AF, Meier WP, Taubert A, Luch A, Reiser G (2012) Effects of silver nanoparticles on primary mixed neural cell cultures: uptake, oxidative stress and acute calcium responses. Toxicol Sci 126:457–468. https://doi.org/10.1093/toxsci/kfs003
98. Liu F, Mahmood M, Xu Y, Watanabe F, Biris AS, Hansen DK, ,Inselman A, Casciano D,Patterson TA, Paule MG, Slikker W Jr, Wang C (2015) Effects of silver nanoparticles on human and rat embryonic neural stem cells. Front Neurosci: https://doi.org/10.3389/fnins.2015.00115.
99. Greish K, Alqahtani AA, Alotaibi AF, Abdulla AM, Bukelly AT, Alsobyani FM, Alharbi GH, Alkiyumi IS, Aldawish MM, Alshahrani TF, Pittalà V, Taurin S, Kamal (2019) The effect of silver nanoparticles on learning, memory and social interaction in BALB/C Mice. Int J Environ Res Public Health: https://doi.org/10.3390/ijerph16010148.
100. Lanone S, Rogerieux F, Geys J, Dupont A, Maillot-Marechal E, Boczkowski J, Lacroix G, Hoet P (2009) Comparative toxicity of 24 manufactured nanoparticles in human alveolar epithelial and macrophage cell lines. Part Fibre Toxicol. https://doi.org/10.1186/1743-8977-6-14
101. Taju G, Abdul Majeed S, Nambi KS, Sahul Hameed AS (2014) In vitro assay for the toxicity of silver nanoparticles using heart and gill cell lines of Catla catla and gill cell line of Labeo rohita. Comp Biochem Physiol C Toxicol Pharmacol 161:41–52. https://doi.org/10.1016/j.cbpc.2014.01.007
102. Trop M, Novak M, Rodl S, Hellbom B, Kroell W, Goessler W (2006) Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J Trauma 60:648–652
103. Mavon A, Miquel C, Lejeune O, Payre B, Moretto P (2007) In vitro percutaneous absorption and in vivo stratum corneum distribution of an organic and a mineral sunscreen. Skin Pharmacol Physiol 20:10-20. https:// doi:https://doi.org/10.1159/000096167.
104. Arora S, Jain J, Rajwade JM, Paknikar KM (2009) Interactions of silver nanoparticles with primary mouse fibroblasts and liver cells. Toxicol Appl Pharmacol 236:310–318. https://doi.org/10.1016/j.taap.2009.02.020
105. Guan R, Kang T, Lu F, Zhang Z, Shen H, Liu M (2012) Cytotoxicity, oxidative stress, and genotoxicity in human hepatocyte and embryonic kidney cellsexposed to ZnO nanoparticles. Nanoscale Res Lett 7:602. https://doi.org/10.1186/1556-276X-7-602
106. Liu H, Ma L, Zhao J, Liu J, Yan J, Ruan J, Hong F (2009) Biochemical toxicity of nano-anatase TiO2 particles in mice. Biol Trace Elem Res 129:170–180. https://doi.org/10.1007/s12011-008-8285-6
107. Zhang XD, Wu D, Shen X, Liu PX, Fan FY, Fan SJ (2012) In vivo renal clearance, biodistribution, toxicity of gold nanoclusters. Biomaterials 33:4628–4638. https://doi.org/10.1016/j.biomaterials.2012.03.020
108. Yan G, Huang Y, Bu Q, Lv L, Deng P, Zhou J, Wang Y, Yang Y, Liu Q, Cen X, Zhao Y (2012) Zinc oxide nanoparticles cause nephrotoxicity and kidney metabolism alterations in rats. J Environ Sci Health A Tox Hazard Subst Environ Eng 47:577–588. https://doi.org/10.1080/10934529.2012.650576
109. Privalova LI, Katsnelson BA, Loginova NV, Gurvich VB, Shur VY, Valamina IE, Makeyev OH, Sutunkova MP, Minigalieva IA, Kireyeva EP, Rusakov VO, Tyurnina AE, Kozin RV, Meshtcheryakova EY, Korotkov AV, Shuman EA, Zvereva AE, Kostykova SV (2014) Subchronic toxicity of copper oxide

nanoparticles and its attenuation with the help of a combination of bioprotectors. Int J Mol Sci 15:12379–12406. https://doi.org/10.3390/ijms150712379
110. Demir E, Burgucu D, Turna F, Aksakal S, Kaya B (2013) Determination of TiO2, ZrO2, and Al2O3 nanoparticles on genotoxic responses in human peripheral blood lymphocytes and cultured embryonic kidney cells. J Toxicol Environ Health A 76:990–1002. https://doi.org/10.1080/15287394.2013.830584
111. Wen H, Dan M, Yang Y, Lyu J, Shao A, Cheng X, Chen L, Xu L (2017) Acute toxicity and genotoxicity of silver nanoparticle in rats. PLoS One. https://doi.org/10.1371/journal.pone.0185554
112. Hoshyar N, Gray S, Han H, Bao G (2016) The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. Nanomedicine (Lond) 11:673–692. https://doi.org/10.2217/nnm.16.5
113. Zhang T, Wang L, Chen Q, Chen C (2014) Cytotoxic potential of silver nanoparticles. Yonsei Med J 55:283–291. https://doi.org/10.3349/ymj.2014.55.2.283
114. Oberdörster G, Oberdörster E, Oberdörster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 113:823–839. https://doi.org/10.1289/ehp.7339
115. He W, Zhou YT, Wamer WG, Boudreau MD, Yin JJ (2012) Mechanisms of the pH dependent generation of hydroxyl radicals and oxygen induced by Ag nanoparticles. Biomaterials 33:7547–7555. https://doi.org/10.1016/j.biomaterials.2012.06.076
116. Yang EJ, Kim S, Kim JS, Choi IH (2012) Inflammasome formation and IL-1β release by human blood monocytes in response to silver nanoparticles. Biomaterials 33:6858–6867. https://doi.org/10.1016/j.biomaterials.2012.06.016
117. Almofti MR, Ichikawa T, Yamashita K, Terada H, Shinohara Y (2003) Silver ion induces a cyclosporine a-insensitive permeability transition in rat liver mitochondria and release of apoptogenic cytochrome C. J Biochem 134:43-49. https:// doi:https://doi.org/10.1093/jb/mvg111.
118. Arora S, Jain J, Rajwade JM, Paknikar KM (2008) Cellular responses induced by silver nanoparticles: in vitro studies. Toxicol Lett 179:93–100. https://doi.org/10.1016/j.toxlet.2008.04.009
119. Wan R, Mo Y, Feng L, Chien S, Tollerud DJ, Zhang Q (2012) DNA damage caused by metal nanoparticles: involvement of oxidative stress and activation of ATM. Chem Res Toxicol 25:1402–1411. https://doi.org/10.1021/tx200513t
120. Foldbjerg R, Dang DA, Autrup H (2011) Cytotoxicity and genotoxicity of silver nanoparticles in the human lung cancer cell line, A549. Arch Toxicol 85:743–750. https://doi.org/10.1007/s00204-010-0545-5
121. Kim KT, Zaikova T, Hutchison JE, Tanguay RL (2013) Gold nanoparticles disrupt zebrafish eye development and pigmentation. Toxicol Sci 133:275–288. https://doi.org/10.1093/toxsci/kft081
122. Valentini X, Absil L, Laurent G, Robbe A, Laurent S, Muller R, Legrand A, Nonclercq D (2017) Toxicity of TiO2 nanoparticles on the NRK52E renal cell line. Mol Cell Toxicol 13:419–431. https://doi.org/10.1007/s13273-017-0046-1
123. Huang YW, Wu CH, Aronstam RS (2010) Toxicity of transition metal oxide nanoparticles: recent insights from in vitro studies. Materials (Basel) 3:4842–4859. https://doi.org/10.3390/ma3104842
124. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M (2006) Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 160:1–40. https://doi.org/10.1016/j.cbi.2005.12.009
125. Zhao X, Rao Y, Liang J, Lin S, Wang X, Li Z, Huang J (2019) Silver nanoparticle-induced phosphorylation of Histone H3 at serine 10 involves MAPK pathways. Biomolecules. https://doi.org/10.3390/biom9020078
126. Zhang J, Qin X, Wang B, Xu G, Qin Z, Wang J, Wu L, Ju X, Bose DD, Qiu F, Zhou H, Zou Z (2017) Zinc oxide nanoparticles harness autophagy to induce cell death in lung epithelial cells. Cell Death Dis 8. https://doi.org/10.1038/cddis.2017.337
127. Vinluan RD 3rd, Zheng J (2015) Serum protein adsorption and excretion pathways of metal nanoparticles. Nanomedicine (Lond) 10:2781–2794. https://doi.org/10.2217/nnm.15.97
128. Zhang YN, Poon W, Tavares AJ, McGilvray ID, Chan WCW (2016) Nanoparticle-liver interactions: cellular uptake and hepatobiliary elimination. J Control Release 240:332–348. https://doi.org/10.1016/j.jconrel.2016.01.020
129. Hadjikhani A, Rodzinski A, Wang P, Nagesetti A, Guduru R, Liang P, Runowicz C, Shahbazmohamadi S, Khizroev S (2017) Biodistribution and clearance of magnetoelectric nanoparticles for nanomedical applications using energy dispersive spectroscopy. Nanomedicine (Lond) 12:1801–1822. https://doi.org/10.2217/nnm-2017-0080
130. Xia T, Kovochich M, Liong M, Zink JI, Nel AE (2008) Cationic polystyrene nanosphere toxicity depends on cell-specific endocytic and mitochondrial injury pathways. ACS Nano 2:85–96. https://doi.org/10.1021/nn700256c
131. Albanese A, Tang PS, Chan WC (2012) The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annu Rev Biomed Eng 14:1–16. https://doi.org/10.1146/annurev-bioeng-071811-150124
132. Sukhanova A, Bozrova S, Sokolov P, Berestovoy M, Karaulov A, Nabiev I (2018) Dependence of nanoparticle toxicity on their physical and chemical properties. Nanoscale Res Lett 13:44. https://doi.org/10.1186/s11671-018-2457-x
133. Hühn D, Kantner K, Geidel C, Brandholt S, De Cock I, Soenen SJ, Rivera Gil P, Montenegro JM, Braeckmans K, Müllen K, Nienhaus GU, Klapper M, Parak WJ (2013) Polymer-coated nanoparticles interacting with proteins and cells: focusing on the sign of the net charge. ACS Nano 7:3253–3263. https://doi.org/10.1021/nn3059295
134. Alexis F, Pridgen E, Molnar LK, Farokhzad OC (2008) Factors affecting the clearance and bio distribution of polymeric nanoparticles. Mol Pharm 5:505–515. https://doi.org/10.1021/mp800051m
135. Zhang Y, Kohler N, Zhang M (2002) Surface modification of super paramagnetic magnetite nanoparticles and their intracellular uptake. Biomaterials 23:1553–1561. https://doi.org/10.1016/S0142-9612(01)00267-8
136. Cheyne RW, Smith TA, Trembleau L, McLaughlin AC (2011) Synthesis and characterisation of biologically compatible TiO2 nanoparticles. Nanoscale Res Lett 6:423. https://doi.org/10.1186/1556-276X-6-423
137. Lee YK, Choi E-J, Webster TJ, Kim S-H, Khang D (2014) Effect of the protein corona on nanoparticles for modulating cytotoxicity and immunotoxicity. Int J Nanomedicine 10:97–113. https://doi.org/10.2147/IJN.S72998
138. Niikura K, Matsunaga T, Suzuki T, Kobayashi S, Yamaguchi H, Orba Y, Kawaguchi A, Hasegawa H, Kajino K, Ninomiya T, Ijiro K, Sawa H (2013) Gold nanoparticles as a vaccine platform : influence of shape and size on immunological responses in vitro and in vivo. ACS Nano 7:3926-3938. https:// doi: https://doi.org/10.1021/nn3057005.
139. Kim J, Park Y, Lee S, Seo J, Kwon D, Park J, Yoon TH, Choi K (2013) Effects of size, impurities, and citrate capping on the toxicity of manufactured silver nano-particles to larval zebrafish (Danio rerio). J Environ Health Sci 39:369–375. https://doi.org/10.5668/JEHS.2013.39.4.369
140. Larsen ST, Jackson P, Poulsen SS, Levin M, Jensen KA, Wallin H, Nielsen GD, Koponen IK (2016) Airway irritation, inflammation, and toxicity in mice following inhalation of metal oxide

nanoparticles. Nanotoxicology 10:1254–1262. https://doi.org/10.1080/17435390.2016.1202350
141. Schmalz G, Hickel R, van Landuyt KL, Reichl FX (2018) Scientific update on nanoparticles in dentistry. Int Dent J 68: 299-305. https:// doi: https://doi.org/10.1111/idj.12394.
142. George GN, Singh SP, Hoover J, Pickering IJ (2009) The chemical forms of mercury in aged and fresh dental amalgam surfaces. Chem Res Toxicol, 22:1761–1764. https://doi.org/10.1021/tx900309c
143. Siddharth R, Gautam R, Chand P, Agrawal KK, Singh RD, Singh BP (2015) Quantitative analysis of leaching of different metals in human saliva from dental casting alloys: an in vivo study. J Indian Prosthodont Soc 15:206–210. https://doi.org/10.4103/0972-4052.164906
144. Van Landuyt KL, Yoshihara K, Geebelen B, Peumans M, Godderis L, Hoet P, Van Meerbeek B (2012) Should we be concerned about composite (nano-) dust? Dent Mater 28:1162–1170. https://doi.org/10.1016/j.dental.2012.08.011
145. Van Landuyt KL, Hellack B, Van Meerbeek B, Peumans M, Hoet P, Wiemann M, Kuhlbusch TA, Asbach C (2014) Nanoparticle release from dental composites. Acta Biomater 10:365–374. https://doi.org/10.1016/j.actbio.2013.09.044
146. Heintze SD (2006) How to qualify and validate wear simulation devices and methods. Dent Mater 22: 712–734. https:// doi: https://doi.org/10.1016/j.dental.2006.02.002.
147. Shi H, Magaye R, Castranova V, Zhao J (2013) Titanium dioxide nanoparticles: a review of current toxicological data. Part Fibre Toxicol. https://doi.org/10.1186/1743-8977-10-15
148. Franchi M, Bacchelli B, Martini D, Pasquale VD, Orsini E, Ottani V, Fini M, Giavaresi G, Giardino R, Ruggeri A (2004) Early detachment of titanium particles from various different surfaces of endosseous dental implants. Biomaterials 25:2239–2246
149. Flatebø RS, Høl PJ, Leknes KN, Kosler J, Lie SA, Gjerdet NR (2011) Mapping of titanium particles in peri-implant oral mucosa by laser ablation inductively coupled plasma mass spectrometry and high-resolution optical darkfield microscopy. J Oral Pathol Med 40: 412–420. https:// doi:https://doi.org/10.1111/j.1600-0714.2010.00958.x.
150. Jacobs JJ, Gilbert JL, Urban RM (1998) Corrosion of metal orthopaedic implants. J Bone Joint Surg Am 80:268–282. https://doi.org/10.2106/00004623-199802000-00015
151. He X, Reichl FX, Wang Y, Michalke B, Milz S, Yang Y, Stolper P, Lindemaier G, Graw M, Hickel R, Högg C (2016) Analysis of titanium and other metals in human jawbones with dental implants - a case series study. Dent Mater 32:1042–1051. https://doi.org/10.1016/j.dental.2016.05.012
152. Gosau M, Haupt M, Thude S, Strowitzki M, Schminke B, Buergers R (2016) Antimicrobial effect and biocompatibility of novel metallic nanocrystalline implant coatings. J Biomed Mater Res B Appl Biomater 104:1571–1579. https://doi.org/10.1002/jbm.b.33376
153. Wang J, Zhou G, Chen C, Yu H, Wang T, Ma Y, Jia G, Gao Y, Li B, Sun J, Li Y, Jiao F, Zhao Y, Chai Z (2007) Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. Toxicol Lett 168:176–185. https://doi.org/10.1016/j.toxlet.2006.12.001
154. Fung MC, Bowen DL (1996) Silver products for medical indications: risk-benefit assessment. J Toxicol Clin Toxicol 34:119–126
155. Feng X, Chen A, Zhang Y, Wang J, Shao L, Wei L (2015) Application of dental nanomaterials: potential toxicity to the central nervous system. Int J Nanomedicine 10:3547–3565. https://doi.org/10.2147/IJN.S79892
156. Kim KT, Lee JY, Kim DD, Yoon IS, Cho HJ (2019) Recent progress in the development of poly(lactic-co-glycolic acid)-based nanostructures for cancer imaging and therapy. Pharmaceutics. https://doi.org/10.3390/pharmaceutics11060280
157. Cai X, Lee A, Ji Z, Huang C, Chang CH, Wang X, Liao YP, Xia T, Li R (2017) Reduction of pulmonary toxicity of metal oxide nanoparticles by phosphonate-based surface passivation. Part Fibre Toxicol 14:13. https://doi.org/10.1186/s12989-017-0193-5