How to Cite:
Barjoee, S. S., & Fathi, A. (2022). A systematic review on the applications of nanoparticles in dentistry. *International Journal of Health Sciences*, *6*(S6), 4864–4876.
https://doi.org/10.53730/ijhs.v6nS6.11472

A systematic review on the applications of nanoparticles in dentistry

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Abstract---Background: Nanotechnology plays a very important role in producing dental compounds. In recent years, a variety of nanoparticles have been used to enhance the properties of these compounds. However, less attention has been paid to the implications of the toxic effects of metallic nanoparticles. The purpose of this systematic review was to review studies evaluating the toxic effects of metal nanoparticles used in dentistry to determine whether long-term use of these compounds has toxic effects. Methods: Electronic search of studies in Pubmed, Scopus, Medline, and google scholar databases was performed until December 2020, according to PRISMA guidelines (preferential reporting items for systematic review and meta-analysis). Results: During the initial research, 325 papers were collected. After reviewing the texts, eliminating duplicates, and applying inclusion criteria, only 10 of these were selected for qualitative review. The results of the studies showed that the use of short-term metallic nanoparticles does not result in increased cytotoxicity. Conclusion: Dental compounds containing metallic nanoparticles had higher cytotoxic activity than unmodified raw materials, but overall, during the short-term review, these studies did not indicate a significant difference in cytotoxicity.

Keywords---nanotechnology, nanoparticles, dentistry, metal nanoparticles.

Introduction

Metals are widely used for a variety of dental materials. The use of metallic compounds in prostheses alters the elastic effects and increases the strength and durability of restorations in the oral cavity (Slokar, Pranjić, & Carek, 2017). A variety of metals are used in dental medicine, including gold, silver, palladium, platinum, copper, zinc, titanium, nickel, chrome, zirconium, beryllium, boron, and aluminum (Gettleman, 1991). These metals may be used on their own or in alloys for restorations and dentures. Recently, nano metal particles have been used in different dental compositions (Schmalz, Hickel, van Landuyt, & Reichl, 2017).Certain metal nanoparticles, in addition to enhancing mechanical and physical properties, also have an antimicrobial character. As a consequence, they can also be used to inhibit plaque biofilm. In orthodontics, nanoparticles have been used in various applications such as arc wires, adhesives, temporary anchors, and biofilm control (Govindankutty, 2015).

For example, to enhance the strength of orthodontic adhesives, nanoparticles containing silver, gold, zirconium, and titanium were used (Al-Nafori, Mohamed, & Wael, 2017; Ramazanzadeh et al., 2015). In addition, orthodontic supports containing silver, copper, and zinc nanoparticles have antibacterial and antibiofilm properties (Felemban & Ebrahim, 2017). Nanoparticles were also used to reduce friction between wires and media (Govindankutty, 2015; Redlich et al., 2008). The size of these nanoparticles is less than 100 nm, which increases the area-volume ratio and therefore reactivity and biological activity (Morones et al., 2005). The release of metal ions results in the antibacterial character of these compounds (Sirelkhatim et al., 2015). These compounds can even produce reactive oxygen species that inactivate them through reaction with bacterial membranes. In addition, their abnormal crystal structure plays a role in increasing their antibacterial properties (Sirelkhatim et al., 2015).

While metallic nanoparticles enhance mechanical performance and antimicrobial properties, no information is available on the long-term toxicological effects of these metallic nanoparticles (Yildirimer, Thanh, Loizidou, & Seifalian, 2011). Chemical and physical damage, chewing abrasion, microbial activity, changes in temperature and pH can alter these compounds (Chaturvedi & Upadhayay, 2010; Faria et al., 2009). It causes the release of metal ions into the mouth cavity. These ions are small and may penetrate cells or general circulation (Behzadi et al., 2017). And provoke cytotoxicity and inflammatory reactions (Besinis, De Peralta, Tredwin, & Handy, 2015). Many factors play a role in the rate of response in cells, such as size, shape, and surface load. Because in dentistry, to increase the antibacterial and mechanical properties, a lot of attention has been paid to metallic nanoparticles, The objective of this review is to assess the potentially toxic effects of the use of metal nanoparticles in dentistry.

Materials and Methods

Study Design

This study was designed based on the Cochrane (Green & Higgins, 2011) criteria for systematic review and reported cases as per the Preferred Reporting Elements

for Systematic Reviews and Meta-analyzes (PRISMA) (Page et al., 2021). Electronic searches of PubMed / MEDLINE, google scholar, Cochrane, and Scopus databases were completed until November 2020. The research question was whether the use of compounds containing metallic nanoparticles in dental restorations enhances their toxicity.

Inclusion Criteria

The eligibility criteria included all full-text English-language studies assessing the toxic effects of materials containing metallic nanoparticles.

Exclusion Criteria

Recommendations, systematic reviews, expert statements, case reports, and non-related papers were excluded.

Search strategy

Electronic databases such as MEDLINE, PubMed, Scopus, Google Scholar, and Cochrane were searched. Another manual search covering the period 2000 to 2020 was also conducted manually in dental journals. Search terms used are a combination of keywords such as "nanometals" or "nano" or "silver" or "titanium" or "gold" or "platinum" or "palladium" or "zinc" or "copper" or "zirconia" or "Nickel" or "oxides" and dentistry."

Data Extraction

A total of 325 articles were searched (Figure 1).

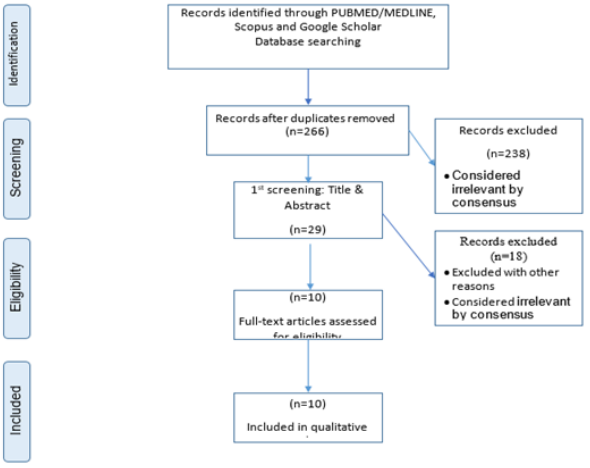

Figure 1. Flow charts for the studies were identified, displayed, and included in the study

The initial screening of articles was based on title and abstract and resulted in the removal of 238 unrelated articles and 59 duplicates. After evaluating the full text of the remaining 29 articles, 18 more studies were deleted. Finally, the full

text of the 10 main studies was included in this review (Akay, Cevik, Karakis, & Sevim, 2018; Chan, Zhang, & Cheung, 2015; Garcia-Contreras et al., 2014; Hashimoto et al., 2016; Heravi et al., 2013; Laiteerapong, Reichl, Hickel, & Högg, 2019; Tabari, Hosseinpour, Parashos, Khozestani, & Rahimi, 2017; Takamiya et al., 2016; Zand et al., 2016; Zhao et al., 2018).

Table 1
Characteristics of the most important information of the selected studies

Author (year), Study Type	Aim of Study	Nanoparticle type	Cell line	Cell viability assays	Conclusions
(Heravi et al., 2013) ***In vitro***	Investigated cytotoxicity of orthodontic adhesive containing 1 wt% TiO2 NPs	TiO2 NPs	HGF L929	MTT	•Both adhesives → moderate toxicity to HGF cells on the first day • Significantly lower toxicity with TiO2 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 TiO2 NPs adhesive had lower toxicity than control • Incorporation of 1 wt% TiO2 NPs → no additional health hazard
(Garcia-Contreras et al., 2014) ***In vitro***	Investigated the possible cytotoxicity and pro inflammation effect of three different powdered GICs (base, core build and restorative) prepared with and without TiO2 NPs	TiO2 NPs	HCS-2 HSC-3 HSC-4 Ca9-22 HGF HPC HPLF	MTT, ELYSA	•Cancer cells exhibited moderate cytotoxicity after 48 h of incubation, regardless of the type of GIC and the presence or absence of TiO2 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 TiO2 NPs
(Chan et al., 2015) ***In vitro***	Evaluated the cytotoxic effect of a novel AgNP endodontic irrigant and compared with 3% sodium hypochlorite	AgNPs	hPDLSCs, NIH 3T3	MTT	AgNP irrigant was non-cytotoxic to both NIH 3T3 and hPDLSCs
(Takamiya et al., 2016) ***In vitro, Animal study***	to determine the cytotoxicity of different types of silver nanoparticles on mouse fibroblast cell line L929 and the reaction of subcutaneous connective tissue of Wistar rats	AgNPs	L929	MTT	AgNPs were not cytotoxic at 25 μg/mL or lower concentrations
(Hashimoto et al., 2016) ***In vitro***	evaluated the inhibition of matrix metalloproteases (MMPs) and cellular responses elicited by gold (Au) and platinum (Pt) nanoparticles (NPs)	AuNPs, PtNPs	L929	RT-qPCR, MMP	No inflammatory responses (production of interleukin-6 and tumor necrosis factor-alpha) to NPs were identified by RT-qPCR. The negative surface charge of NPs (COOH(-)) binds to the Zn(2+) of the MMP active center by chelation, leading to MMP inhibition. Gold nanoparticles are plausible candidates for MMP inhibitors in resin-bonding materials because they effectively inhibit MMP-1 activity without cytotoxic or inflammatory effects
(Zand et al., 2016) ***Animal study***	Evaluated the subcutaneous inflammatory reaction of rat	AgNPs	tissues of male rat		•No significant difference in the inflammatory reactions between the groups • Incorporation of 1% AgNPs to MTA does not affect the inflammatory

	connective tissues to white MTA with and without AgNPs				reaction of subcutaneous tissue in rat models
(Tabari et al., 2017) ***In vitro***	to assess and compare the cytotoxicity of four metal oxide nanoparticles (TiO2, SiO2, ZnO, and Al2O3) on human dental pulp stem cells	TiO2 SiO2 ZnO Al2O3	DPSCs	MTT	The minimum cell viability was observed in ZnO followed by TiO2, SiO2 and Al2O3. The higher concentration and longer duration of exposure increased cellular death
(Akay et al., 2018) ***In vitro***	Evaluated the cytotoxicity of different kinds of NPs added to two types of maxillofacial elastomers	TiO2 NPs	L-929	MTT	•TiO2 NPs, fumed silica, and silaned silica added to a commercial silicone-based elastomer were nontoxic
(Zhao et al., 2018) ***In vitro***	To address the toxicity of dental alloys and silver nanoparticles, an in vivo-like LO2 3-D model was constructed within polyvinylidene fluoride hollow fiber materials to mimic the microenvironment of liver tissue.	AgNPs	LO2	MTT	the toxicity of both the castings and the coated silver nanoparticles aggravated as time increased, yet the nanoparticles attenuated the general toxicity by preventing metal ion release, especially at high concentrations.
(Laiteerapong et al., 2019) ***In vitro***	Formulated and investigated the genotoxic effect of novel GICs containing ZrNPs and micro-particles on DNA double-strand breaks of human gingival fibroblasts (HGFs)	ZrO2 NP	HGFs	XTT, IFA	•GIC and both Zr modified GICs had no genotoxic effect on HGFs

Strategy to assess the quality of studies

In each article, variables such as author, year of publication, type of study, type of metal nanoparticles, cell line, toxicity tests used, and conclusions were recorded (Tables 1).The search results were obtained in an electronic database selected by two independent researchers. The studies were selected by two investigators based on the title and content of the summary. In case of disagreement, a third researcher was consulted to solve the problem. Selected papers for the evaluation were reviewed and their reference list consulted.

Data analysis

After the initial review of the selected articles, due to the observed large heterogeneity in the type of study design, data collection methods between studies, at the discretion of the author, quantitative data analysis and meta-analysis were not performed. Therefore, more descriptive data were analyzed (Dehkordi et al. 2011a; Dehkordi et al. 2011b; Dehkordi et al. 2012a; Dehkordi et al. 2012b; Dehkordi et al. 2012c; Dehkordi et al. 2013a; Dehkordi et al. 2013b; Dehkordi et al. 2013c).

Results

Selection of studies and flow chart

Out of 325 identified articles, 59 were deleted due to duplication, and after the initial screening of titles and abstracts, another 238 articles were deleted. The full text of the remaining 29 studies was obtained and reviewed, and as a result, 18 other articles were excluded from the study due to the lack of focus of publications on the target compounds (6 studies), non-addition of nanoparticles to dental materials (5 studies) and inconsistency of study objectives with the research question (number of studies); Finally, 10 studies met all inclusion criteria and were included in the qualitative evaluation. The flow chart (Figure 1) shows the selection process of the studies.

Qualitative analysis

The addition of nanoparticles to dental compounds to increase the effectiveness and durability of restorations has recently received much attention. In the present systematic study, 10 articles were reviewed. Eight in vitro studies and two in animal models evaluated the toxic effects of metal nanoparticles used in dentistry (Akay et al., 2018; Chan et al., 2015; Garcia-Contreras et al., 2014; Hashimoto et al., 2016; Heravi et al., 2013; Laiteerapong et al., 2019; Tabari et al., 2017; Takamiya et al., 2016; Zand et al., 2016; Zhao et al., 2018).

Nano-metal poisoning used in dentistry

The first studies on the use of nanoparticles in dental materials were published between 2006 and 2008 (Beyth et al., 2008; Beyth, Yudovin-Farber, Bahir, Domb, & Weiss, 2006; Yudovin-Farber et al., 2008), but in recent years Much attention has been paid to it. Compounds such as Ag, TiO_2, ZnO, and Au are commonly

used in dental compounds. Among different types of metal nanoparticles, silver nanoparticles were the most used in studies. Some studies have shown that these nanoparticles have no toxic effects on the surrounding cells. For example, the results of using Ag nanoparticles for 48 hours had no toxic effects on the cell line of hPDLSCs and mouse fibroblasts (Chan et al., 2015). In another study, Ag nanoparticles incorporated into MTA had no toxic reaction on rat connective tissue [65]. According to the results of one study, GICs containing Zr nanoparticles had no toxic effects (Zand et al., 2016). Although TiO_2-containing compounds are considered non-toxic, some studies have shown toxic effects on human gingival fibroblast cells (Akay et al., 2018; Garcia-Contreras et al., 2014). Most of the articles presented in this systematic review agreed that the use of nanoparticles in dental restorative compounds does not increase their toxicity compared to unmodified materials (Akay et al., 2018; Chan et al., 2015; Hashimoto et al., 2016; Laiteerapong et al., 2019; Takamiya et al., 2016; Zand et al., 2016). However, the results of several studies failed to report a significant association between nanoparticle composition and cytotoxic deficiency.

Discussion

Medical scienes have extensive developed in the recent years (Dehkordi et al. 2014a; Dehkordi et al. 2014 b; Dehkordi et al. 2014 c; Dehkordi et al. 2017 ab; Dehkordi et al. 23017b; Safarpordehkordi et al. 2014a; Safarpor Dehkordi et al. 2014b; Safarpor Dehkordi et al. 2014c; Nejat et al. 2015; Ghorbani et al. 2016; Ranjbar et al. 2019a; Rahi et al. 2020; Ranjbar et al. 2019b; Mashak et al. 2020; Abdolmaleki et al. 2019; Ranjbar et al. 2020). Based on a review of sources in this study, few studies were found to investigate the toxic effects of metal nanoparticles on humans, especially in dental compounds. The results of short-term laboratory studies show that dental materials containing metal nanoparticles are not cytotoxic (Akay et al., 2018; Chan et al., 2015; Garcia-Contreras et al., 2014; Heravi et al., 2013; Laiteerapong et al., 2019). Since dental compounds remain in the oral cavity for a long time, there is a possibility of these compounds penetrating the saliva and causing systemic complications (Besinis et al., 2015). Based on the available evidence, these compounds during their presence in the oral cavity, due to abrasion and erosion caused by chewing, undergo biodegradation which causes dissolution in saliva (Morones et al., 2005). On the other hand, when using compounds containing alloys, a stable balance is created in the oral cavity that the alloy may remain elemental or oxidize. The uncharged elements present in the alloy may be converted to positively charged ions by the loss of electrons and enter the saliva. These positive ions can affect the surrounding tissues or enter the bloodstream (Elshahawy & Watanabe, 2014). Therefore, long-term study of the toxic effects of metal nanoparticles seems necessary. In this systematic review, no studies were found that examined the effects of toxicity in the long term, and all studies examined these effects in the short term (Akay et al., 2018; Chan et al., 2015; Garcia-Contreras et al., 2014; Heravi et al., 2013; Laiteerapong et al., 2019; Zand et al., 2016). In addition to duration, various other parameters can affect the toxicity effects of nanoparticles (Saifi, Khan, & Godugu, 2018)

For example, the size of nanoparticles plays an important role in the development of cellular and immunological responses (Hoshyar, Gray, Han, & Bao, 2016). The

smaller size of the nanoparticles increases the surface-to-volume ratio and thus increases their chemical reaction. According to the results of some studies, reducing the size of nanoparticles from 30 nm to 3 nm increases the number of surface particles from 5 to 50%, which also increases the likelihood of their reactivity (Oberdörster, Oberdörster, & Oberdörster, 2005; Saifi et al., 2018). There is some evidence that small metal nanoparticles such as Ag can easily enter the cell and nucleus and alter DNA activity and cell viability (Saifi et al., 2018; J. Zhang et al., 2017; T. Zhang, Wang, Chen, & Chen, 2014). After the nanoparticles enter the cell, the reticuloendothelial system directs them to the liver and spleen (Vinluan III & Zheng, 2015). These nanoparticles are then filtered by the kidneys. Based on the evidence, it has been found that most nanoparticles are cleared from the body and less than 5% of nanoparticles are involved in causing disease (Y.-N. Zhang, Poon, Tavares, McGilvray, & Chan, 2016). In general, nanoparticles smaller than 10 nm are cleared by the kidneys and larger than 200 nm by the spleen (Hadjikhani et al., 2017). Metal nanoparticles used in dental materials are in this range and can play a role in the toxicity of the reticuloendothelial system.

The surface charge of metal nanoparticles is also an important factor in determining their toxicity because cationic nanoparticles are more reactive than anionic and are easily absorbed by cells (Albanese, Tang, & Chan, 2012; Saifi et al., 2018; Xia, Kovochich, Liong, Zink, & Nel, 2008). The reason for this is also related to the negative charge of the cell membrane (He, Zhou, Wamer, Boudreau, & Yin, 2012). These nanoparticles are also able to attach to and damage negatively charged DNA (Sukhanova et al., 2018). The surface charge nature of nanoparticles used in dentistry is cationic, so they may enter the cell, cause toxicity and stimulate immunogenic reactions (Lee, Choi, Webster, Kim, & Khang, 2015).

Although due to the stability and biocompatibility of these compounds are used in dental permanent restorations, but the destruction of the compounds used or improper use, can cause toxic compounds (Besinis et al., 2015). For example, there have been reports of toxic effects from the use of amalgams and metal alloys (George, Singh, Hoover, & Pickering, 2009; Siddharth et al., 2015). However, there are no similar results in dentistry for compounds containing metal nanoparticles. Long-term metal nanoparticles may cause cellular or systemic toxicity. These effects have been studied in different studies in laboratory and animal conditions in the short term (Akay et al., 2018; Chan et al., 2015; Garcia-Contreras et al., 2014; Hashimoto et al., 2016; Heravi et al., 2013; Laiteerapong et al., 2019; Tabari et al., 2017; Takamiya et al., 2016; Zand et al., 2016; Zhao et al., 2018) (Table 1).

Conclusion

There is a possibility of direct contact of nanoparticles with cells of the oral cavity and the occurrence of allergic reactions or inflammation in the individual because the cells of oral tissue are mainly of the stratified squamous epithelium type. Therefore, despite the wide range of studies on the use of nanotechnology in dentistry, qualitative studies included in this study do not show a long-term effect of metal nanoparticles cytotoxic. However, the criteria for the duration of

follow-up in the use of compounds containing metal nanoparticles in the long run, need to be further studied.

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