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Clinical Use of Nanoparticles in Orthodontics as Possible Aid to Reduce the Incidence of White Spot Lesions

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Abstract: *In the recent years, the number of patients treated with fixed orthodontic appliances is permanently increasing, as well as their interest for esthetic treatment issues. One potential unwanted consequence of orthodontic therapy is the onset of white spot lesions on teeth enamel during treatment. The present review includes studies published between 2010 and 2021 on three different databases (Science Direct, PubMed, Google Scholar) regarding the implications of nanoparticles in white spots prevention. The initial databases search identified 471 entries. Following the PRISMA-P 2015 guide, 39 scientific articles were selected for full text evaluation. The studies were divided into four categories. The interpretation of studies included in this review permits us to sustain the idea that the use of nanoparticles in various orthodontic materials improves their bioactivity, decreases the biofilm appearance around components of the fixed appliances, and can even initiate remineralization in the enamel proximity. Most of the analysed articles are in-vitro studies of new biomaterials properties, in the recent years depicting an increase interest of the researchers towards randomized control trials regarding clinical use of new orthodontic biomaterials.*

Keywords*: nanoparticles, orthodontics, white spot lesions, composite polymers, enamel protection*

1. Introduction

Orthodontics is a specific medical discipline dedicated to malocclusions treatment. Anthropological studies suggest that in the ultramodern populations the frequence of malocclusions increases, their prevalence being several times lesser currently nowadays than it was only a few hundred years ago [1]. Severe clinical forms of malocclusions can sometimes be perceived as social impairment. Under these circumstances, the orthodontic therapy is progressively popular all over the world; more patients seek to improve the quality of their life, by making positive changes on their facial appearance and dental esthetics [2].

In addition, it's not considered a fully successful treatment, if the esthetic result of the orthodontic therapy isn't adequate. The treatment objectives are accomplished with the aid of orthodontic appliances (fixed or removable ones), which move teeth through the bone. The orthodontic fixed appliances are retained on teeth surfaces for the entire treatment process through brackets on labial teeth surfaces (metallic or ceramic) and bands, covering all surfaces of posterior teeth (metallic). The attachments (brackets and bands) are collated on the teeth surfaces (frequently the labial surfaces) with the aid of orthodontic cements. The brackets are then interconnected with the archwire (stainless steel or nickel-titanium archwire) that generates the needed orthodontic forces for malocclusion correction. The archwire is connected into brackets with ligatures: steel ties (made of stainless steel) or elastomeric ties (products made of latex or polyurethanes). At the end of the active phase of treatment, the orthodontic fixed appliances are removed from teeth surfaces through specific medical procedures by the physician.

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After brackets/bands removal, unsightly areas of decalcification on teeth enamel may be observed. These decalcification regions are designated as “white spot lesions” and are represent an undesirable secondary effect of orthodontic treatment, caused by the demineralization of enamel surfaces around brackets or bands. If the organic acids produced by certain saliva bacteria remain on the tooth enamel for a specific period of time, areas of localized decalcification may appear. According to previously published statistical data, the teeth most frequently affected by enamel demineralization are the superior incisors, especially the maxillary lateral ones. 36% of 338 patients treated in a university orthodontic clinic had at least one lesion on a maxillary incisor tooth at the end of treatment despite preventive efforts. The threat factors for decalcifications were youngish age at the beginning of treatment, and deficient oral hygiene ahead and during orthodontic fixed therapy [3]. Different studies suggest that decalcification areas can be detected 1 month after the fixed appliance placement and that approximately 50-75% of patients wearing fixed orthodontic appliances are at threat to present a number of white spot lesions during treatment [4].

Among preventative clinical measures against potential enamel demineralization areas during orthodontic treatment the scientific literature suggests a series of measures: the use of products with fluoride or calcium, the mouth rinses with chlorhexidine, the modification of the patient’s diet [5]. One major disadvantage of these measures is the necessary compliance of the patient, that is often questionable, especially for children and teenagers.

In order to override these difficulties, researches were conducted towards novel and effective approaches to prevent the onset of white spot lesions. In the last decades, the nanoparticles were successfully used as antimicrobial agents in multiple areas of dentistry [6].

The scientific literature describes two main mechanisms of using the biomaterials antimicrobial effects of nanoparticles in orthodontic components: by combining them with materials such as composites, glass ionomers, or by using them as coatings on the material surfaces. Orthodontic biomaterials, obtained through nanoparticles mixing or coating, such as adhesives, bands, brackets, arch wires, even ligatures and supplements of oral hygiene (mouthwashes, varnishes) have been subjects of experimental tests.

One proposed method to prevent white spot lesions was the clinical use of a bonding agent that could inhibit bacterial growth or the replacement of the orthodontic classical cement with a resin-modified glass ionomer (RMGI) cement that has the capacity to release ions of fluor [7-9]. Other modified orthodontic cements are capable of inducing enamel remineralization by releasing high levels of Ca and P ions [10]. Some researchers showed that, due to their small size and increased surface area, the nanomaterials included into orthodontic cements could decrease the germs growth around orthodontic brackets and improve the capacity of the cement to prevent decalcification [11].

Some researchers proposed the surface coating of brackets and archwires with titanium oxide, as a photocatalyst oxide film. The titanium oxide participates to some chemical reactions (oxidation and reduction reactions) in the presence of a watery medium (saliva) and ultraviolet light; during these chemical processes the titanium oxide releases radicals of hydroxyl, that are further responsible for the degradation of organic substances retained on the metallic components surfaces [12].

Elastomeric ligatures, being placed in close proximity to the enamel surface and regularly replaced during the orthodontic treatment could represent a potentially useful carrier for localized antimicrobial agents, delivered to prevent white spot lesions onset [13].

Since the elimination of plaque is regarded as an important therapeutic strategy to prevent white spot lesions, preventive measures, apart from the routine oral hygiene measures, were tested: the local use of antimicrobial products, remineralization materials with calcium, varnish with fluoride, chlorhexidine, xylitol [14]. A recent study proposed the use of nano-hydroxyapatite serum on intact enamel, prior to bonding procedure, as a preventive agent for enamel demineralization [15].

The aim of this review is to investigate the latest outcomes regarding the use of nanoparticles on different orthodontic materials in order to prevent the onset of white spot lesions.

2. Materials and methods

2.1. Articles search

Articles search was conducted on three different databases (Science Direct, PubMed, Google Scholar), for research studies published between 2010 and 2021. For accuracy purposes, the steps of the databases search performed for the present review preparation were similar to those described in "Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols" (PRISMA-P 2015) [16].

2.2. Search terms

In order to find appropriate articles, a combination of the following search terms was used: "nanoparticles", "orthodontics"," white spot lesion", "enamel protection", "demineralization prevention". In this review we included scientific full-text articles published between 2010 and 2021, written in English.

2.3. Articles selection

Figure 1 comprises the flow diagram of this review. With automation tools we selected from databases only the research articles: in Science Direct remained 33 articles, in PubMed 23 articles, in Google Scholar 89 articles. After this step, we manually compared the titles from all 3 databases and all the duplicated records were identified and removed (32 items from the Science Direct selection and 9 articles from the PubMed selection). The titles and abstracts of the remaining 104 articles were independently evaluated by the authors, in order to exclude the selection bias.

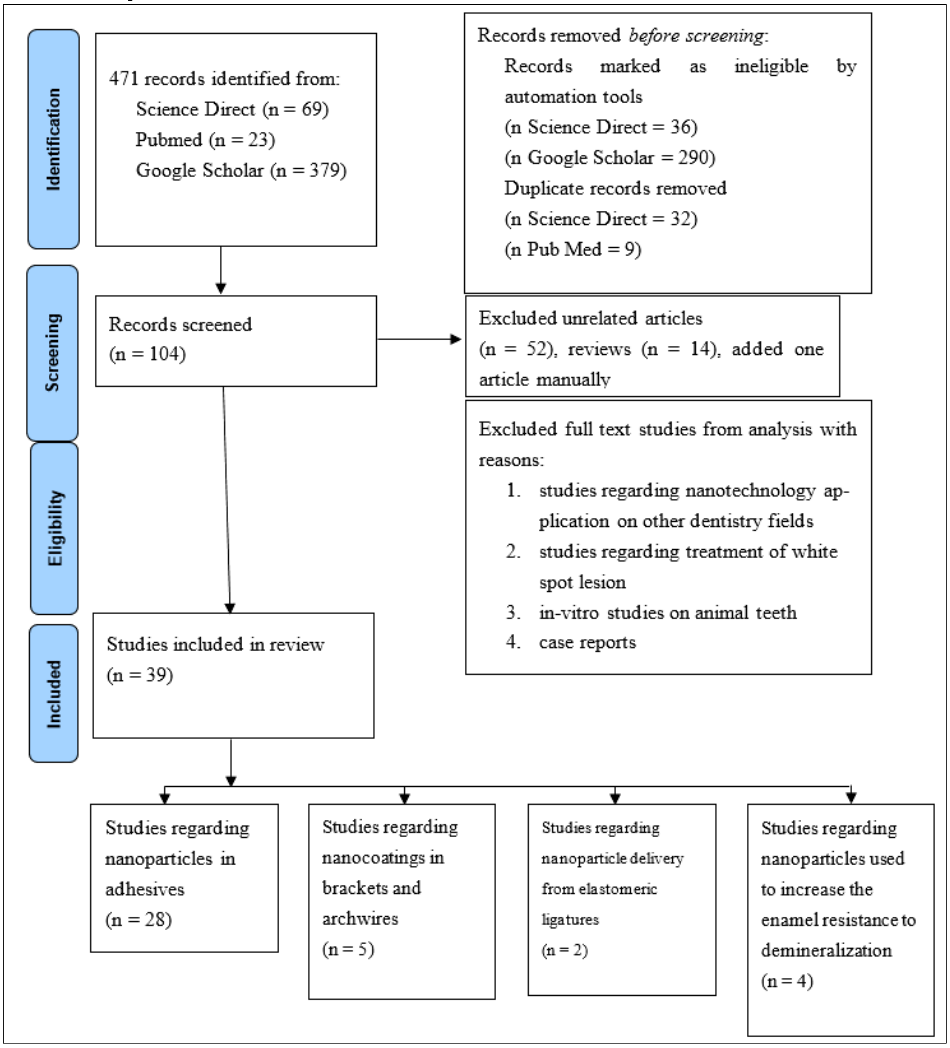

Figure 1. PRISMA flow diagram for research stages

2.4. Inclusion criteria

The inclusion criteria were:

- original research studies regarding prevention of the white spot lesions during orthodontic treatment through innovative materials with nanoparticles (in-vitro experimental studies and clinical randomized studies),
- articles describing novel developed orthodontic materials intended to prevent white spot lesions appearance with the aid of nanotechnologies.

2.5. Exclusion criteria

We excluded from the databases duplicated articles, prior reviews on the subject in question, animal studies, case reports, studies regarding nanotechnology application on other dentistry fields, studies regarding white spot lesions treatment with biomaterials.

3. Results and discussions

The initial databases search returned 471 scientific records written in English: 69 titles in Science Direct database, 23 titles in PubMed database and 379 entries in Google Scholar database. Using the automation tools form Science Direct and Google Scholar (we automatically eliminated review articles, encyclopedia, book chapters, conference abstracts, examinations, mini reviews) 326 records were marked as ineligible. After the search for duplicated items we removed 9 articles from the PubMed selections and 32 articles form the Science Direct selection. The rest of 104 articles were evaluated through abstract reviewing, one more article related to our subject was manually added. Following the inclusion parameters on the abstracts of these articles, resulted a pool of 39 articles. Their full texts were carefully evaluated and the studies were then included into four categories:

- Studies regarding nanoparticles in adhesives;
- Studies regarding nanocoatings in brackets and archwires;
- Studies regarding nanoparticle delivery from elastomeric ligatures;
- Studies regarding the use of nanoparticles as a mean to increase the tooth resistance to decalcification.

3.1. Studies regarding nanoparticles in adhesives

The two adhesive materials used primarily for attaching bands and brackets to teeth surfaces are composites and glass ionomer cements. Nanoparticles mixed in the orthodontic adhesives improve their mechanical qualities and reduce the risk of enamel demineralization [6].

Ahn et al. compared by in vitro tests an experimental composite material enhanced with silver nanoparticles and silica nanofillers with two commercial available adhesives (one composite and one RMGI) [17]. In order to quantify the antimicrobial features of the new product, the study tested the adhesion of Streptococcus mutans and Streptococcus sobrinus to the orthodontic adhesives. The results of the experiments indicate that mixing silver nanoparticles and nanofillers into composite adhesive can contribute to the prevention of enamel demineralization lesions around brackets without altering thequality of the bonding strength of the novel composite.

In a study published in 2015, Altmann and coworkers presented and tested an experimental orthodontic adhesive mixed with different amounts of 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT). This research evaluated a series of new product's physical properties, and assayed its antibacterial activity against Streptococcus mutans germs. The new composite polymers provoked a decrease in germ proliferation, especially the products containing 15% and 20% TAT [18].

Whang et al. selected a commercial RMGI cement (Fuji ORTHO LC; GC Corporation, Tokyo, Japan) as the parent system for the manufacturing of a new adhesive [19]. In this cement the researchers incorporated 0.05% and 1% silver nanoparticles (NAg). The study results suggested that the sample of the novel cement containing 0.1% NAg inhibited the germs on the enamel surface, and also the germ proliferation in the medium of culture away from the surface.

Moreira et al. studied a new orthodontic band cement with antimicrobial properties, developed through a chemical process generating silver nanoparticles in situ [20]. They added to a commercial available cement with silver nanoparticles (Opal Band Cement) benzoyl peroxide (0.5, 1.0, 1.5, or 2.0 %) and 2,2-(p-Tolylimino) diethanol (0.5 or 1%). The novel modified orthodontic band cement has better antimicrobial effect against Streptococcus mutans and Lactobacillus acidophilus when compared to the effect of the commercial cement; the results showed that the higher the benzoyl concentration is, the greater becomes the antimicrobial effect (best for 0.5 and 1 % benzoyl samples).

Zhang et al. proposed for the first time the combination of RMGI cement with two antimicrobial agents, 2-methacryloyloxyethyl phosphorylcholine (MPC) and silver nanoparticles, aiming to develop a modified orthodontic cement with improved clinical benefits: antibacterial and protein-repellent capabilities [21]. The mixing of a combination of 3% MPC and 0.1% NAg into a RMGI cement inhibited the bacteria proliferation on the surface of the tested new material, and also inhibited the germs grown away from the material in the culture medium. In authors opinion, this experimental results prove the material potential capacity to prevent white spot lesions underneath the orthodontic bracket and in the proximal areas.

Further evaluating these types of new polymers obtained by incorporating 0.1% NAg, 3% MPC, and 1.5% dimethylaminohexadecyl methacrylate (DMAHDM) into a RMGI cement (Vitremer, 3 M, St. Paul, MN), Zhang and coworkers tested its mechanical properties (enamel bond strength, adhesive remnant index), the protein-repellent and anti-biofilm effect, the human saliva germs biofilm proliferation and the lactic acid elimination [22]. According to this study results, the above mentioned cement mixed with three bioactive agents (NAg, MPC and DMAHDM) notably decreased the protein adsorption and germs persistence on tooth surface, however without decreasing enamel shear bond strength.

In a different research, Zhang et al. mixed in the same as above commercial RMGI 0.1% NAg, 3% MPC as protein-repellent agent, 1.5% DMAHDM as antibacterial substance, and various amounts (10-20%) of amorphous calcium phosphate nanoparticles (NACP) (Vitremer, 3 M, St. Paul, MN) [23]. They also added in the product another component, a new resin manufactured from triethylene glycol dimethacrylate (TEGDMA) and bisphenol A glycidyl dimethacrylate (BisGMA) to help the incorporation of NACP into the RMGI matrix. Testing these new orthodontic cements, the authors concluded that increasing the NACP filler level the Ca and P ions were released on larger quantities. The tests results showed that the combination of MPC, DMAHDM and NAg reduces the amount of biofilm and acid formation compared to commercial available RMGI.

The research published by Sodagar et al. tested the antibacterial properties of a conventional orthodontic bonding (Transbond XT, 3 M, Monrovia, CA, USA) mixed with three different concentrations (1%, 5% and 10 %) of silver/hydroxyapatite nanoparticles (Ag/HA N) [24]. The antimicrobial activity of the new composites was investigated in vitro by comparing the numbers of viable populations of Streptococcus mutans, Lactobacillus acidophilus, and Streptococcus sanguinis after specific trial periods of 3 days, 15 days and 30 days. The authors concluded that the composites with 5 % Ag/HA N were responsible for the onset of bacterial growth inhibition areas and presented antibacterial properties against biofilms, without decreasing the required mechanical qualities of the composite adhesive.

Ma and coworkers described a new bioactive orthodontic cement with simultaneously antibacterial, protein-repellent and remineralizing properties: MPC, DMAHDM, and NACP were incorporated into a commercial available RMGI (GC Ortho LC, Fuji) [25]. The experimental products were tested using polarized light microscopy for enamel lesion depth, after inducing the demineralization process with the aid of an in-vitro created dental plaque biofilm model. The test results showed that the new resin containing NACP, MPC and DMAHDM substantially reduced enamel demineralization in the proximity of orthodontic brackets.

Liu et al. proposed two orthodontic experimental adhesives manufactured on a base consisting of 39.5% ethoxylated bisphenol A dimethacrylate (EBPADMA) and 44.5% pyromellitic glycerol dimethacrylate (PMGDM) [26]. For the fabrication of the first orthodontic experimental adhesive in this matrix 5% 2-methacryloxylethyl dodecyl methyl ammonium bromide (MAE-DB), a polymerizable quaternary ammonium salt, was added. The second experimental orthodontic adhesive was obtained by mixing a supplemental weight fraction of 40% NACP. The authors tested the antibacterial activity of the newly developed materials, and they also assessed their potential remineralization effect on the enamel surfaces. A commercial orthodontic adhesive (Transbond XT Light Cure Adhesive) was selected as control material for tests; the experimental material with 5% MAE-DB and 40% NACP presented important reduction in biofilm appearance and prevented enamel decalcification.

Toodehzaeim et al investigated the effects of incorporating nanoparticles of copper oxide (CuO) on the antimicrobial qualities and the bond strength of commercial available orthodontic adhesives [27]. They evaluated an orthodontic composite (Transbond XT) modified with copper oxide (CuO) nanoparticles in several concentrations (0.01, 0.5, and 1.0 %). The authors concluded that incorporating copper oxide nanoparticles into the orthodontic composite added antimicrobial effects to the adhesive with no adverse effects on shear bond strength.

Yi et al. proposed the development of a new orthodontic cement by incorporating 5-30% calcium fluoride nanoparticles ($nCaF_2$) and DMAHDM (1-4%) for increased antibacterial and remineralization capabilities [28]. The tests conducted in-vitro on extracted teeth proved that the fluor release was greatly increased with the addition of calcium fluoride nanoparticles and that the remineralization capability of resin-modified glass ionomer cements and enamel hardness were significantly increased by the new orthodontic cement as compared with commercial controls (Transbond XT, 3 M, Monrovia, CA, USA and GC Ortho LC, Fuji, Aichi-ken, Japan). According to this study results, the antibacterial effects of the RMGI cements was substantially enhanced by the combined use of 20% $nCaF_2$ and 3% DMAHDM.

Further research on orthodontic cements with calcium fluoride nanoparticles (5-30%) regarded improvement of long-term and high levels of F releasing, investigated the possibility of material F recharging and the physical and cytotoxic properties of the new enhanced products [29]. The researchers proposed two types of experimental matrix resin; the first resin compound was obtained by blending equal quantities of ethoxylated bisphenol A dimethacrylate (EBPADMA) and pyromellitic glycerol dimethacrylate (PMGDM). For the second matrix resin, 5% bisphenol A glycidyl dimethacrylate (BisGMA) and 10% 2-hydroxyethyl methacrylate (HEMA) were added into the previously described polymer. Into both matrices was then incorporated the $nCaF_2$ at different mass fractions: 0%, 20% and 30%. As control for the experiments the researchers selected the commercial available RMGI GC Ortho LC (Fuji, Aichi-ken, Japan). For the fluor recharging process, the samples were immersed in a sodium fluoride solution for 1 min once weekly. The authors presented the second matrix resin with 30% $nCaF_2$ as the first rechargeable $nCaF_2$ orthodontic cement with clinically acceptable biocompatibility.

The study published by Nam et al. evaluates an orthodontic bonding adhesive (Transbond XT Low Flow) modified with bioactive glass containing 2.5% fluoride. The bioactive glass was added at variable ratios: 1, 3, and 5% [30]. The study assessed the biological cytotoxicity of the products, several mechanical properties of the new materials by means of Vickers hardness test, the test of bracket retention, the adhesive remnant index, the antibacterial activity of the new products on germs of Streptococcus mutans and the anti-decalcification effect of the adhesives. The authors concluded that orthodontic bonding adhesive modified with fluorinated bioactive glass nanoparticles demonstrated physical and biological stability, higher concentration-dependent anti-bacterial activity and an excellent anti-demineralization effect.

Garcia et al. developed a series of experimental orthodontic adhesives (EOA) using different concentrations of the ionic liquid 1-n-butyl-3-methylimidazoilium bis(trifluoromethanesulfonyl)imide ($BMIM.NTf_2$) and further evaluated them [31]. These EOA were manufactured as mixed materials containing 25% triethylene glycol dimethacrylates (TEGDMA) and 75% bisphenol A glycidyl methacrylate (BisGMA). The authors evaluated the physical and chemical properties of the prepared composites (polymerization behaviour, softening in solvent, ultimate tensile strength, shear bond strenght, thermogravimetric analysis, cytotoxicity) and their antimicrobial activity against biofilm formation and planktonic bacteria. The results showed that all orthodontic adhesives with ionic liquid presented antibacterial activity and decreased the biofilm formation compared to control.

Pourhajibagher and coworkers evaluated the antimicrobial properties of an orthodontic adhesive incorporating various percents (1.2%, 2.5%, 5%, 7.5% and 10%) of cationic curcumin doped zinc oxide nanoparticles (cCur/ZnONPs) against cariogenic bacteria including Streptococcus mutans, Streptococcus sobrinus, and Lactobacillus acidophilus [32]. The addition of cCur/ZnONPs into the orthodontic adhesive and its photo-activation is presented by the authors as an adequate method to increase the antimicrobial activity of conventional orthodontic adhesive through the localized inhibition of bacterial activity in the surface of biofilm. The appropriate concentration of cCur/ZnONPs was set at 7.5%, as the maximal limit for preserving adequate shear bond strength.

In the study published in 2019, Firzok and coworkers used for addition to resin-based composites (RBC) two types of bioactive glasses ceramics nanoparticles, designated as BGC-1 and BGC-2, and compared them with similar polymers with F ions; F-BGC-1 and F-BGC-2. As RBC the authors used a commercial available orthodontic bonding, Transbond-XT (3 M ESPE, Germany) [33]. After the improvement of the resin-based composite with few drops of ethanol, 5.0 % of the experimental powders (BGC-1, BGC-2, F-BGC-1, F-BGC-2) were added separately and incorporated for homogenization. The research tested the capacity of these modified resins to initiate recalcification processes on the enamel surface. The composites enriched with fluor ions provided better results concerning enamel remineralization than the simple composite adhesives without fluoride. The authors concluded that the fluoride powder mixed with Transbond-XT represents the best combination among all tested samples, aimed to decrease the number of potential white spot lesions around brackets.

Noori and Kareem assessed the antibacterial properties and the capacities to decrease the biofilm formation of conventional glass-ionomer cement (GIC) modified by mixing nanoparticles of magnesium oxide (MgO). The authors used as GIC powder Ketac Molar Easymix and different concentrations of MgO nanoparticles (0%, 1%, 2.5%, 5%, and 10%) [34]. In order to determine the antibacterial activity of the new cement, the research used the agar disk diffusion method on brain-heart infusion. The results suggested that the antibacterial and antibiofilm properties of GIC material could be improved by the addition of MgO nanoparticles. The antibacterial effect of the newly developed material is positively correlated with the amount of the nanoparticles mixed into the cement matrix.

The in-vitro study conducted by Kotta et al. aimed to evaluate the antibacterial activity of a new composite containing TiO_2 nanoparticle by comparing it to the antimicrobial effect of a conventional known composite [35]. The tested bacterial species were represented by Streptococcus mutans and Lactobacillus acidophilus germs. The composite with 1% nanoparticles of TiO_2 presented a statistically significant increase in antibacterial activity and a significant decrease in number of both bacterial colonies, when compared with the antimicrobial effect of the commercial available composite.

Yassaei et al. compared the antibacterial effects of composites manufactured by adding different nanoparticles to orthodontic adhesive on the proliferation of Streptococcus mutans at different period of times [36]. They added hydroxyapatite (HA), titanium oxide (TiO), zinc oxide (ZnO), copper oxide (CuO) and silver (Ag) nanoparticles (0.5% and 1% weight concentrations), to the light cure commercial available orthodontic bonding agent Transbond XT (3M Unitek, Monrovia, California, USA). The results suggested no significant statistical differences between HA containing composites and control groups; hydroxyapatite nanoparticles provided a lower antibacterial effect than zinc; the addition of 1% CuO and 1% Ag oxide to composites provided antibacterial properties only for limited time periods. The authors concluded that the clinical use of copper oxide and silver oxide nanoparticles cannot be justified.

Ahmadi and coworkers evaluated the anti-biofilm activity of an orthodontic adhesive incorporating 3, 5, 7, or 10 % curcumin (Cur) enhanced with nanoparticles of Poly lactic-co-glycolic acid (Cur-PLGA-NPs). The results of the in-vitro study suggested that the 7 % Cur-PLGA-NPs can serve as an orthodontic adhesive antimicrobial additive [37].

Park et al. evaluated the antibacterial and remineralization effects of mixing 2-methacryloyloxyethyl phosphorylcholine (MPC) and mesoporous bioactive glass nanoparticles (MBN) at various ratios with orthodontic bonding agents [38]. As parent system, the authors used a commercial orthodontic bonding, CharmFil-Flow. The amounts of mixed nanoparticles into the orthodontic bondings were 3% MPC, 5% MPC, 3% MPC + 3% MBN, and respectively 3% MPC + 5% MBN. The study evaluated the mechanical properties (microhardness, shear bond strength), the biological properties (cell viability, protein adsorption, anti-bacterial properties on Streptococcus mutans and Escherichia coli.) and anti-demineralization properties of novel polymers as compared to the original commercial orthodontic bonding. The results indicated that the combination of MPC and MBN to orthodontic bonding agents improves anti-demineralization, protein-repellent and antibacterial abilities of the new materials.

A recent study described the mechanical and biological properties of a novel self-adhesive resin containing 3-5% mesoporous bioactive glass nanoparticles (MBNs) and 1-3% 2-methacryloyloxyethyl phosphorylcholine (MPC) [39]. Bioactive glasses release calcium and phosphorus ions and promote enamel remineralization by facilitating the appearance of hydroxyapatite. The MBNs also presents the capacity to load other biomolecules, and the MPC reduces the protein adsorption and bacterial adhesion on teeth surfaces. The study results indicated that all types of combined self-adhesive resins presented increased antibacterial activity and anti-demineralization effect than commercial control. The most important anti-decalcification effect was registered by testing the sample with 3% MBN.

Sánchez-Tito and Tay evaluated the antibacterial property of the modified orthodontic resin with different concentrations of NAg (0.05%, 0.1%, 0.5%, 1%), and quantified its preventive effect on the appearance of white spot lesions [40]. The study results demonstrated that the mixing of 0.5% and 1% NAg into the resin inhibited the proliferation of Streptococus mutans and Lactobacillus acidophilus. Regarding the demineralization of the enamel, the modified orthodontic resins with 0.1% or higher concentrations of NAg presented protective capacities and avoided the white spot lesions appearance.

Farzanegan et al conducted a randomized clinical trial study on 24 orthodontic patients wearing fixed appliances, aimed to investigate the effect of the addition of chitosan nanoparticles and TiO_2 nanoparticles on Streptococcus mutans counts and the enamel mineral content in patients [41]. They compared one orthodontic experimental adhesive (Transbond XT modified with 1% chitosan nanoparticles and 1% TiO_2 nanoparticles) and the commercial available Transbond XT (3M Unitek, USA). They analyzed the maxillary lateral incisor and upper second premolar teeth, counting the Streptococus mutans germs with real-time PCR test and measuring the enamel mineral content. These tests were performed 1 day, 2 months, and 6 months after bonding the brackets on the teeth surfaces. The study results showed that the mixing of chitosan and TiO_2 nanoparticles into orthodontic adhesives promotes usefull antibacterial effect, and causes no significant differences between the enamel mineral compositions in the experimental group and in the control group.

Ghorbanzadeh et al. evaluated the physicomechanical and antimicrobial potency against Streptococus mutans of orthodontic composite (Transbond XT) containing nanostructured graphene oxide (nGO) (OC-nGO) as a novel composite. The nanoparticles were used in different concentrations (1%, 2%, 5%, and 10% nGO) [42]. The researchers recorded for the new orthodontic composite with 5% nGO the highest shear bond strength values, and proved that it possesses antimicrobial and anti-biofilm properties.

Behnaz et al. tested the mixing of ZnO and TiO_2 nanoparticles into an orthodontic bonding (Transbond XT) for preventing white spot lesions [43]. They conducted an in vitro experimental study on extracted premolars stored in a controlled environment with exposure to Streptococus mutans germs. They assessed weekly possible white spot lesions using DIAGNOdent and photography. These procedures where repeted for 4 weeks. The results of this study showed that adding TiO_2 and ZnO nanoparticles to Transbond XT determined a decrease in enamel demineralization and incidence of white spots, and depicted no significant differences between protective effects triggered by TiO_2 composites and by ZnO bondings.

Al Tuma and Yassir proposed a novel orthodontic primer that incorporates $nCaF_2$ and investigated, together with some physical properties (homogeneity, agglomeration, cytotoxic behavior, shear bond strength and adhesive remnant index), the material potential to promote enamel remineralization process when used with the conventional acid etching technique [44]. The matrix used by the authors was the commercial available orthodontic primer Transbond XT (3M-Unitek, Monrovia, USA); they added to this material 5%, 10%, or 20% $nCaF_2$ (Nanoshell Company, USA). The remineralization and anti-carious effect of the novel primer were indirectly assessed, the authors assuming that the homogenous distribution of nCaF2 within the primers with no apparent agglomeration after four months of preparation and the adequate shear bond strength could facilitate the remineralization process.

The studies regarding nanoparticles in adhesives included in the present review are presented in Table 1.

Table 1. Studies regarding nanoparticles in adhesives included in the present review

Authors	Study type	Tested new material	Commercial control materials	Compared properties	Outcome
Ahn et al. (2009) [17]	In vitro study on 85 human premolars	Experimental orthodontic adhesives (EOA) with NAg and silica nanofillers	Transbond XT (3 M/Unitek, Monrovia, CA, USA) Fuji Ortho LC (GC Corporation, Tokyo, Japan)	Physical properties and antibacterial activities against cariogenic streptococci	EOA can help prevent enamel demineralization around their surfaces without compromising physical properties
Altmann et al. (2015) [18]	In vitro study on agar Petri dishes containing brain-heart infusion (BHI)	EOA + 10%/15%/20% TAT	EOA without TAT	Antibacterial activity against Streptococcus mutans	EOAs showed antibacterial activity, especially those with 15% and 20% TAT
Wang et al. (2015) [19]	In vitro study on 80 upper first premolars	Orthodontic cement (Fuji ORTHO LC; GC Corporation, Tokyo, Japan) + 0.05% Nag/ 0.1% NAg	Transbond XT (3M Unitek, Monrovia, CA, USA) Fuji ORTHO LC (GC Corporation, Tokyo, Japan)	Antibacterial effects on the cement surface and at the distance in the medium of culture	The 0.1% NAg cement inhibited the germs on the surface, and the bacterial proliferation at the distance in the culture medium
Moreira et al. (2015) [20]	In vitro study on cement poured into a mold between two glass slides	NAg-loaded orthodontic band cement + Ag benzoate (AgBz 0.5%, 1.0%, 1.5%, or 2.0%) and 2,2-(p-Tolylimino) diethanol (0.5 or 1 %)	Opal Band Cement (Ultradent Products Inc, South Jordan, UT)	Antibacterial activity against Streptococcus mutans and Lactobacillus acidophilus	NAg containing orthodontic cement has better antimicrobial properties, increasing with the AgBz concentration, (best for 0.5 and 1 % AgBz samples)
Zhang et al. (2015) [21]	In vitro study on extracted first premolars	RMGI cement (Vitremer) + 0.1% NAg + 3% MPC	Transbond XT (3 M, Monrovia, CA) Vitremer (3M, St. Paul, MN)	Protein adsorption and antibacterial capabilities	The new cement has strong antibacterial effect and presents protein-repellent properties
Zhang et al (2016) [22]	In vitro study on 180 extracted human first premolars, McBain artificial saliva medium and resin disk molds in 24-well plates	RMGI cement (Vitremer) + 3% MPC + 0.1% NAg + 1.5% DMAHDM	As non-bioactive control = Transbond XT (3M, Monrovia, CA, USA) As fluoride-releasing control = Vitremer (3M, St. Paul, MN, USA)	Mechanical and protein-repellent properties, anti-biofilm effect, impact on biofilm proliferation and lactic acid discharge	RMGI modified cement decreased the protein adsorption and biofilm persistence, without affecting the enamel shear bond strength of the adhesive.
Zhang et al. (2016) [23]	In vitro study on 120 extracted first premolars	RMGI cement (Vitremer) + 1.5% DMAHDM + 3% MPC + 0.1% NAg + (0-20)% NACP + 15% BisGMA-TEGDMA	Transbond XT (3 M, Monrovia, CA) Vitremer (3 M, St. Paul, MN)	Capacity of Ca and P ion release, protein adsorption	The cement enhanced with NACP releases Ca and P ions and decreases the biofilm proliferation

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Sodagar et al (2016) [24]	In vitro study on Mueller Hinton agar plates	Orthodontic adhesive + 1%, 5%, and 10 % Ag/HA N	Transbond XT (3M Unitek, Monrovia, California, USA)	Antibacterial properties against Streptococcus mutans, Lactobacillus acidophilus, and Streptococcus sanguinis	Orthodontic adhesives with 5 % Ag/HA N exhibited antibacterial properties against biofilm
Ma et al. (2017) [25]	In vitro study on 96 freshly extracted premolars	95.5% RMGI GC Ortho LC (Fuji) + 3% MPC + 1.5% DMAHDM / 60.5% RMGI + 1.5% DMAHDM + 3% MPC + + 20% NACP + 15% BisGMA-TEGDMA	RMGI GC Ortho LC (Fuji) Transbond XT (3 M Unitek, Monrovia, California, USA)	The consequences on enamel hardness and demineralization depth	The adhesive with MPC, DMAHDM and NACP was more efficient in protecting enamel, when compared to control materials
Liu et al. (2018) [26]	In vitro study on 80 human premolars	EOA (44.5% PMGDM + 39.5% EBPADMA) with 5% MAE-DB/ 5% MAE-DB + 40% NACP	Transbond XT Light Cure (3 M Unitek, Monrovia, CA, USA)	Antibacterial properties against Streptococcus mutans, the potential for enamel remineralization	EOA with 5% MAE-DB + 40% NACP presented important reduction in biofilm proliferation and prevented demineralization
Toodehzaeim et al. (2018) [27]	In vitro study on 40 maxillary premolars	Orthodontic composite (Transbond XT) + 0.01%, 0.5%, and 1.0% CuO nanoparticles	Transbond XT (3M Unitek, Monrovia, California, USA)	Antibacterial activity against Streptococus mutans and the quality of shear bond strength	Incorporating CuO nanoparticles into the orthodontic composite added antimicrobial effects, without altering the shear bond strength of the material
Yi et al. (2019) [28]	In vitro study on extracted premolars and wisdom teeth	Orthodontic cement (GC Ortho LC) + $nCaF_2$ (5-30%) + DMAHDM (1-4%)	GC Ortho LC (Fuji, Aichi-ken, Japan) Transbond XT(3 M Unitek, Monrovia, CA, USA)	The physical and chemical properties	The mixing of 20% $nCaF_2$ and 3% DMAHDM into GC orthodontic cement presented best antibacterial and remineralization properties
Yi et al. (2019) [29]	In vitro study on 84 premolars	PMGDM + EBPADMA + $nCaF_2$ + glass/ PMGDM + EBPADMA + HEMA + BisGMA + $nCaF_2$ + glass	GC ortho LC (Fuji, Japan)	Cytotoxicity, enamel shear bond strength, F ions recharge and release	PMGDM + EBPADMA + HEMA + BisGMA + 30%$nCaF_2$ + glass was the first rechargeable $nCaF_2$ orthodontic cement with clinically acceptable biocompatibility
Nam et al. (2019) [30]	In vitro study on 20 extracted premolars and resin disks in 96-well plates	Orthodontic bonding adhesive (Transbond Supreme LV) + bioactive glass containing 2.5% fluoride at ratios of 1%, 3%, and 5%	Transbond Supreme LV Low Viscosity Light Cure (3M, Monrovia, CA, USA)	Mechanical properties (Vickers hardness test, bracket retention test, adhesive remnant index), biological cytotoxicity, antibacterial activity on Streptococcus mutans and anti-demineralization effect	Orthodontic bonding adhesive modified with fluorinated bioactive glass nanoparticles demonstrated physical and biological stability, higher concentration-dependent anti-bacterial activity and an excellent anti-demineralization effect
Garcia et al. (2019) [31]	In vitro study on 48 plates after the photoactivation of samples	EOA (75% BisGMA and 25 % TEGDMA) + 5%/10%/15% $BMIM.NTf_2$	EOA without $BMIM.NTf_2$	Antibacterial activity against planktonic Streptococcus mutans	All orthodontic adhesives with $BMIM.NTf_2$ presented antibacterial activity and decreased the biofilm formation compared to control.
Pourhajibagher et al. (2019) [32]	In vitro study on 60 maxillary first premolars	Orthodontic adhesive (Transbond XT) + (1.2%, 2.5%, 5%, 7.5% or 10%) cCur/ZnONPs	Transbond XT (3 M Unitek, Monrovia, CA)	Antimicrobial activity against Streptococcus mutans, Streptococcus sobrinus, and Lactobacillus acidophilus	The photo-activated adhesive with 7.5% cCur/ZnONPs can inhibit the growth of multispecies biofilm

Firzok et al. (2019) [33]	In vitro study on 150 human extracted premolars	Ortodontic adhesive (Transbond-XT) + 5% BGC-1/ BGC-2/F-BGC-1/F-BGC-2	Transbond-XT (3 M ESPE, Germany)	The ability to promote a process of remineralization on enamel surface	Transbond-XT mixed with F-BGC-2 provided best results in reducing the number of white spot lesions around brackets
Noori and Kareem (2019) [34]	In vitro study on BHI agar plate	Glass-ionomer cement (Ketac Molar Easymix) + 1%, 2.5%, 5%, and 10% MgO nanoparticles	Transbond XT	The antibacterial and antibiofilm properties	The cement with MgO nanoparticles presents better antibacterial and antibiofilm properties; this effect is positively correlated with the percentage of the nanoparticles added
Kotta et al. (2020) [35]	In vitro study on Mueller Hinton agar plates	Composite (Enlight) containing 1%TiO_2 nanoparticles	Enlight, Ormco, CA	Antibacterial activity against Streptococcus mutans and Lactobacillus acidophilus	TiO_2 containing composite showed a statistically significant increase in antibacterial activity.
Yassaei et al. (2020) [36]	In vitro study on enriched Mueller-Hinton agar	Light cure orthodontic composite (Transbond XT) + HA, TiO_2, ZnO, CuO and Ag oxide nanoparticles (0.5% and 1%)	Transbond XT (3M Unitek, Monrovia, California, USA)	Antibacterial effects on Streptococcus mutans at different times (3, 15, 30 days)	Addition of 1% CuO and 1% silver oxide to composites has only short-term antibacterial effects
Ahmadi et al. (2020) [37]	In vitro study on 50 maxillary first premolars	Orthodontic bonding adhesive (Transbond XT) + 3, 5, 7, and 10 % Cur-PLGA-NPs,	Transbond XT (3 M Unitek, Monrovia, CA)	The anti-biofilm activity	Adhesive with 7 % Cur-PLGA-NPs presents biocompatibility and antimicrobial effects.
Park et al. (2020) [38]	In vitro study on 50 human premolars	Flowable resin for orthodontic bonding + 3-5% MPC and 3-5% MBN	CharmFil-Flow (Denkist, Gunpo, South Korea)	Mechanical, biological and anti-demineralization properties, antibacterial properties on Streptococcus mutans and Escherichia coli	The combination of MPC and MBN to orthodontic bonding agents improves anti-demineralization, protein-repellent and antibacterial abilities
Choi et al. (2021) [39]	In vitro study on 20 premolars	Self-adhesive resin Ortho Connect Flow (GC Corp, Tokyo, Japan) + 3-5% MPC +/- 1-3% MBN	Ortho Connect Flow (GC Corp, Tokyo, Japan)	Antibacterial test against Streptococcus mutans, anti-demineralization test	All experimental groups showed statistically reduced values of Streptococus germs compared to the control group on days 1 and 3. The 3% MBN group exhibited the best anti-decalcification effect
Sánchez-Tito and Tay (2021) [40]	In vitro study on 45 premolars and agar diffusion test on Petri dishes	Modified orthodontic resin with different concentrations of silver-nanoparticles (1%, 0.5%, 0.1%, and 0.05% NAg)	Transbond XT (3M Unitek, Monrovia, California, USA)	Preventive effect on white spot lesions, antibacterial activity against Streptococcus mutans and Lactobacillus Acidophilus.	Incorporation of 0.5% and 1% NAg into orthodontic resin provides an important antimicrobial activity against Streptococcus mutans and Lactobacillus acidophilus. The incorporation of 0.1% or more NAg was effective against demineralization and white spot lesions formation
Farzanegan et al. (2021) [41]	Double-blind randomized clinical trial study on 24 patients with fixed orthodontic treatment (upper second premolars and maxillary lateral incisors)	Orthodontic adhesive (Transbond XT) + 1% chitosan nanoparticles + 1% TiO_2 nanoparticles	Transbond XT (3M Unitek, Monrovia, California, USA)	Antibacterial effect on Streptococcus mutans, assessment of the mineral composition of the enamel	Incorporation of chitosan and TiO_2 nanoparticles in orthodontic composites induces an antibacterial property, with no significant differences between enamel mineral content for the experimental group and control group

Ghorbanzadeh et al. (2021) [42]	In vitro study on fabricated composite discs	Orthodontic composite (Transbond XT) + nGO (1%, 2%, 5%, and 10%)	Transbond XT	The physicomechanical and antimicrobial potency against Streptococus mutans	The new orthodontic composite with 5% nGO exhibited the highest shear bond strength values, antimicrobial and anti-biofilm properties
Behnaz et al. (2021) [43]	In vitro study on 43 human premolar teeth	Orthodontic bonding (Transbond XT) + ZnO/+ TiO_2	Tansbond XT	Preventing white spot lesions	Transbond XT bonding with TiO_2/ZnO nanoparticles decreased the occurrence of enamel lesions and the incidence of white spot lesions
Al Tuma and Yassir (2021) [44]	In vitro study on 48 upper premolars	Orthodontic primer modified (Transbond XT primer) with calcium fluoride nanoparticles (5%, 10%, 20% $nCaF_2$)	Transbond™ XT primer (3M Unitek, Monrovia, California, USA)	Cytotoxic and physical properties	Orthodontic primers with the tested concentrations of $nCaF_2$ presented homogenous distribution of $nCaF_2$ within the primers, with no apparent agglomeration after four months of preparation, acceptable cytotoxic level, adequate shear bond strength and adhesive remnant index

3.2.1. Studies regarding nanocoatings in brackets

Regarding brackets material enhancement, Cao et al. studied the technical possibility of depositing a thin pellicle of titanium dioxide (TiO_2) on the surface of stainless steel brackets. They presented the radio frequency (RF) magnetron sputtering method as an adequate laboratory procedure. Some physical properties of the new composite product (crystal structure, surface morphology) and its antimicrobial activities against Lactobacillus acidophilus and Candida albicans were tested [45]. The study results indicated that archwires coating with TiO_2 thin film sputtered for 180 min and annealed at 450^oC presented adequate physical characteristics and showed the best antibacterial activity.

Similar, Baby and coworkers tested stainless steel brackets covered with two different phases of photocatalytic TiO_2 (anatase and rutile phases) and evaluated the antibacterial properties and potential cytotoxic effects of these modified brackets [46]. According to tests results, both brackets coated with the anatase and the rutile phases of photocatalytic TiO_2 showed important antimicrobial properties, the rutile phase presenting a significantly greater antimicrobial effect. Regarding potential brackets cytotoxicity, evaluated under controlled laboratory conditions, the products covered with the anatase phase presented slightly cytotoxicity, but the rutile phase brackets had moderate to severe cytotoxic effects. The authors concluded that the anatase phase of titanium oxide could be used for bracket coating, because it showed important antibacterial activity and significantly less cytotoxicity than the rutile phase of the oxide.

Jasso-Ruiz et al. proposed the prevention of white spot lesions by covering the surfaces of orthodontic brackets with Ag nanoparticles, appreciating that the brackets represent an area with a greater accumulation of oral bacteria [47]. In this study the authors used silver nitrate on both ceramic and metal brackets and the silver nanoparticles were synthetized with a chemical method. The antimicrobial effects of the new products were tested and the results demonstrated antibacterial activity of the nanosilver coating against Staphylococcus aureus and Escherichia coli. Due to their antibacterial properties, the orthodontic brackets coated with NAg can represent an efficient method to reduce the incidence of white spot lesions.

The studies regarding nanocoatings in brackets included in the present review are presented in Table 2.

Table 2. Studies regarding nanocoatings in brackets included in the present review

Authors	Study type	Tested new material	Commercial control materials	Compared properties	Outcome
Cao et al. (2014) [45]	In vitro study on Petri dishes	Orthodontic stainless steel brackets (3B, Hangzhou, China) coated with TiO_2 thin films	Uncoated brackets	Physical properties, antimicrobial activities against Lactobacillus acidophilus and Candida albicans.	Archwires covered with TiO_2 thin pellicle under specific circumstances (sputtered for 180 min and annealed at 450^{0}C) showed the best antibacterial activity.
Baby et al. (2017) [46]	In vitro study in tubes with BHI	Stainless brackets (Mini 2000; Ormco, Orange, Calif) coated with the anatase/rutile phase of TiO_2	Uncoated brackets	Antibacterial effect against Streptococcus mutans species and cytotoxicity of TiO_2 coated brackets under controlled laboratory conditions.	Coated brackets presented antibacterial properties, but also cytotoxicity. The rutile phase of TiO_2 presented significantly greater antibacterial effect, but also moderate to severe cytotoxicity. Therefore, the anatase phase of TiO_2 is recommended for clinical use, having good antibacterial property and only slightly cytotoxicity.
Jasso-Ruiz et al. (2019) [47]	In vitro study with Kirby- Bauer disc diffusion method	GI InVu Roth Ceramic bracket (TP Orthodontics, LaPorte, IN, USA), GII System Alexander LTS Stainless steel bracket (American Orthodontics Sheboygan, WI, USA), GIII Gemini Roth Stainless steel bracket (3M Unitek, Corporation Monrovia, CA, USA), GIV Nu-Edge Roth Cr-Co bracket (TP Orthodontics, LaPorte, IN, USA), GV Radiance plus Roth Sapphire bracket (American Orthodontics Sheboygan, WI, USA) coated with NAg	Uncoated brackets	The prevention of white spot lesions, the antimicrobial properties against Staphylococcus aureus and Escherichia coli.	The orthodontic brackets with NAg present antibacterial effect and can prevent the appearance of white spot lesions.

3.2.2. Studies regarding nanocoatings in archwires

The study published by Venkatesan et al. evaluated the benefits of coating the nickel-titanium (NiTi) archwire with titanium dioxide (TiO_2) from the perspective of Streptococcus mutans adhesion and enamel mineralization [48]. The authors used for testing 0.016-in NiTi wires and performed the comparison 1-month post insertion of the archwires. The adhesion of Streptococus mutans germs was significantly decreased on the coated wires as compared with the uncoated ones. The composition of the archwires didn’t influence the mineral content of enamel surrounding the bracket.

Gholami and coworkers used as antimicrobial agents the ZnO nanoparticles and tested the modification of the surface of nickel-titanium (NiTi) wires determined by these nanoparticles [49]. The ZnO nanoparticles exhibited different morphological aspects, correlated with the specific coating methods: coating by chemical vapor deposition, polymer composite coating, chemical precipitation method, electrospinning process and sol-gel synthesis. The study assessed the antibacterial activity of ZnO nanoparticles against Streptococcus mutans using the colony counting method, finding that all tested samples presented antibacterial effects. The antibacterial effects of ZnO nanoparticles were significantly enhanced when the novel product was obtained using the chemical vapor deposition method.

The studies regarding nanocoatings in archwires included in the present review are presented in Table 3.

Table 3. Studies regarding nanocoatings in archwires included in the present review

Authors	Study type	Tested new material	Commercial control materials	Compared properties	Outcome
Venkatesan et al. (2020) [48]	Clinical study on 12 patients	0.016-in NiTi wires (Ormco Corp) coated with TiO_2	Uncoated 0.016-in NiTi wires (Ormco Corp)	The capacity of bacterial adhesion (Streptococus mutans) on the archwires tested with real-time PCR test Enamel mineralization assessed using the DIAGNOdent pen (KAVO Dental Corp, Lake, Zurich, Ill).	The ability of Streptococus mutans to adhere on the archwires was significantly decreased in the coated wires, compared with the uncoated wires. The type of the archwire didn't influence the mineral content of enamel surrounding the bracket.
Gholami et al. (2021) [49]	In vitro study on agar plates with BHI	Nickel-titanium (NiTi) wires coated with ZnO nanoparticles of different morphologies (coating with chemical vapor deposition, chemical precipitation method, polymer composite coating, sol-gel synthesis and electrospinning process)	Uncoated round 0.016-inch orthodontic NiTi straight wires (OthoTechnology, FL, USA)	Assessment of antibacterial activity of ZnO nanoparticles against Streptococcus mutans (colony counting method).	All the samples had antibacterial effects. The antibacterial effects of ZnO nanoparticles were significantly enhanced if they are obtained with the chemical vapor deposition method.

3.3. Studies regarding nanoparticle delivery from elastomeric ligatures

Hernández-Gómora and coworkers proposed the coating of elastomeric ligatures with silver nanoparticles (AgNP) as local antimicrobial agent, proving that these elastic modules can inhibit the growth of Streptococus mutans, Lactobacillus casei, Streptococus aureus and Escherichia coli [50]. Therefore, the composite material could act against dental plaque and decrease the incidence of dental enamel demineralization.

The laboratory study designed by Kamarudin et al. aimed to test elastomeric ligatures coated with chlorhexidine hexametaphosphate (CHX-HMP) as orthodontic material with sustained release of chlorhexidine between orthodontic appointments (usual time range 4-8 weeks) [13]. The results proved that elastomeric ligatures coated with CHX-HMP release soluble CHX continually for more than 8 weeks. This new property of the ligatures can be enhanced by conditioning the product with ethanol.

The studies regarding nanoparticle delivery from elastomeric ligatures included in the present review are presented in Table 4.

Table 4. Studies regarding nanoparticle delivery from elastomeric ligatures included in the present review

Authors	Study type	Tested new material	Commercial control materials	Compared properties	Outcome
Hernández-Gómora et al. (2017) [50]	In vitro study with agar diffusion tests	Orthodontic elastomeric modules coated with silver nanoparticles	Mini Stix ligature ties non-coated, (TP Orthodontics, LaPorte, IN, USA)	Antibacterial properties against Streptococcus mutans, Lactobacillus casei, Staphylococcus aureus and Escherichia coli.	The presence of coated elastomeric ligatures conducted to inhibition halos for all germs.
Kamarudin et al. (2020) [13]	In vitro study with UV spectrophotometry	Orthodontic elastomeric modules coated with CHX-HMP	Polyurethane elastomeric ligatures with occlusal guards (AlastiK; 3M Unitek, Bracknell, United Kingdom)	Temporary release of CHX (over 8 week period) measured using UV Spectrophotometry.	Elastomeric ligatures coated with CHX-HMP release for 10 weeks continually soluble CHX. Better results are obtained by conditioning the product with ethanol.

3.4. Studies regarding the use of nanoparticles as a mean to increase the tooth resistance to decalcification

Abbassy et al. proposed the use of a paste containing 45S5 bioglass and a topical fluoride material as local protective agents against enamel demineralization around orthodontic brackets [51]. They tested the bioglass protective effect on extracted incisors and premolars bonded in vitro with Moisture Insensitive Primer and Transbond PLUS color change adhesive. After 18 minutes' exposure to 1% citric acid, the teeth surfaces were examined by SEM-EDS. The study results showed that the 45S5 bioglass paste application provided an interaction layer that resisted erosion.

The randomized clinical trial conducted by Ali and coworkers intended to compare the effect of mouthwashes with fluoride, chlorhexidine and nanosilver on white spot lesions around fixed orthodontic attachments [52]. During six months in the course of orthodontic treatment, each patient was instructed to use twice daily 5 ml of mouthwash and rinse for one minute. The number of white spot lesions was recorded by clinical inspection before bonding and at 30, 90 and 180 days after bonding of both arches. The results of the study indicated that the mouthwash with silver nanoparticles was more effective regarding white spot lesions reduction than the chlorhexidine and fluoride mouthwashes.

Babanouri and coworkers tested the possibility of using nano-hydroxyapatite (nHAP) serum on intact enamel prior to orthodontic bonding as a caries preventive agent [15]. The tested material was Repairing Serum (PrevDent International BV, Amsterdam, Netherlands), that contains nano-hydroxyapatite; for 10 days it was applied on the enamel surface of extracted teeth for 2–3 minutes and rinsed after 30 minutes with water. The teeth were brushed twice daily and the serum was applied after the second brushing time. The brackets were bonded on the labial teeth surface after etching +/- micro abrasion (the sandblast method). Investigating the effect of high concentration nano-hydroxyapatite on shear bond strength of metal brackets, the authors found indirect evidence of protective capacities of nHAP: the serum use did not affect in vitro the shear bond strength of metal brackets and enamel damages after bracket removal were not detected. A better effect on bond strength was noted when the preparation method for bonding after applying nHAP included micro abrasion. After debonding, less damage to the enamel was encountered if the previous bonding procedure included a sixty seconds etching time.

Poornima et al. conducted a controlled trial to assess the quantity of bacterial plaque formation around orthodontic brackets after the topical application of a varnish with chitosan or a varnish with chlorhexidine and fluoride [14]. The degree of biofilm formation was quantified through the Bonded Bracket Index (Plaque index) prior to bonding and then weekly for 6 weeks. The tested materials were one varnish with chitosan (UNO Gel Bioschell, Germiphene corp., Brantford, Canada) and one varnish with chlorhexidine and fluoride (Cervitec F, Ivoclar Vivadent, Liechtenstein), chosen as a standard of care in this trial. The clinical trial included a varnish application procedure, performed immediately after the clinical session of bracket placement and then weekly, for 6 weeks period. The evaluated arch region was represented by the maxillary teeth enrolled between the right premolar and the left one. The study results demonstrated comparable protective effects of chitosan varnish and chlorhexidine-fluoride varnish regarding plaque control. Both products reduced bacterial proliferation, and the plaque pH remained neutral over a period of six weeks in patients treated with fixed orthodontic appliances.

The studies regarding nanoparticles used to increase the enamel resistance to demineralization included in the present review are presented in Table 5.

Table 5. Studies regarding the use of nanoparticles as a mean to increase the tooth resistance to decalcification included in the present review

Authors	Study type	Tested new material	Commercial control materials	Compared properties	Outcome
Abbassy et al (2019) [51]	In vitro study on 21 freshly extracted incisors and premolars	45S5 bioglass paste, topical fluoride	No enamel protection	Protection against acidic erosion	The 45S5 bioglass paste application provided an interaction layer that resisted erosion.

Ali et al. (2021), [52]	Randomized double-blind clinical trial on 42 patients	NAg mouthwash (CORAL, Carson City, NV, USA)	CHX mouthwash (PERIO.AID, Cerdanyola, Spain) fluoride mouthwash (VITIS)	Protection against white spot lesions	The NAg mouthwash was more efficient in reducing white spot lesions than mouthwashes with CHX and fluoride.
Babanouri and coworkers (2021), [15]	In vitro study on 60 premolars	n-HAP Repairing Serum (PrevDent International BV, Amsterdam, Netherlands)	No enamel protection	Prevention of white spot lesion	The use of nHAP before bracket bonding can represent a caries preventive method.
Poornima et al. (2021), [14]	Clinical study on 20 patients	Chitosan-based varnish (UNO Gel Bioschell, Germiphene corp., Brantford, Canada)	Chlorhexidine-fluoride varnish (Cervitec F, Ivoclar Vivadent, Schaan, Liechtenstein)	Reduction of bacterial plaque formation around brackets.	Both varnishes reduced bacterial count.

After presenting and evaluating the data of the above-mentioned researches, further considerations are required. According to the recently published research outcomes, nanotechnology promises to improve the clinical performances of various dental products. As presented in Figure 2, an important number of studies evaluated the mixing of nanoparticles into orthodontic adhesives, concluding that the future extended clinical use of these novel composite materials may contribute to prevent enamel demineralization and white spot lesions. This result of databases search was expected, since the first approach in using nanoparticles was the incorporation of antibacterial materials to the resin matrix. When applied on teeth surfaces, these nanomaterials are released over time and inhibit local germ proliferation. The quality of bonding between teeth and orthodontic attachments in terms of mechanical aspects represents an important part of successful orthodontic treatment. Altering the chemical structure of orthodontic adhesives may decrease their mechanical properties (enamel bond strength, adhesive remnant index). As discussed above, a series of studies evaluate, together with the antibacterial properties of the novel composite biomaterial, its mechanical properties [22].

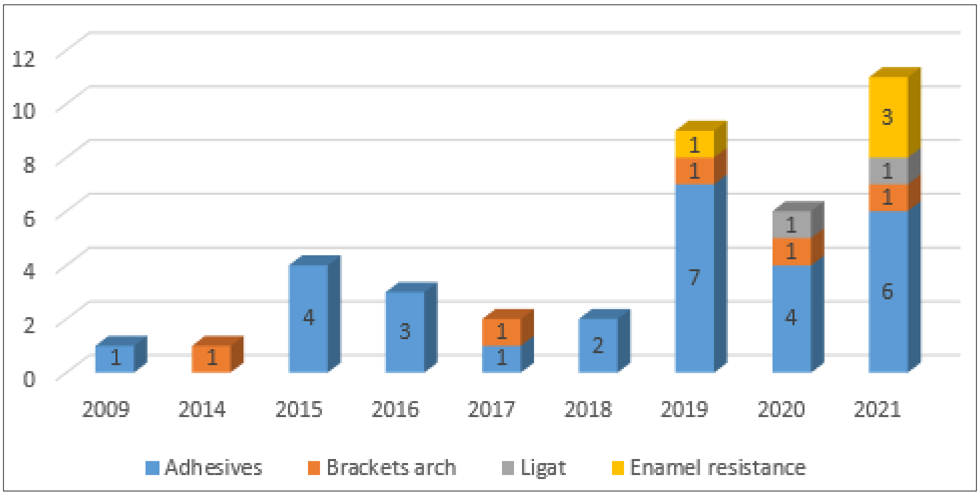

Figure 2. Articles distribution, related to research subjects and publishing year

Some researchers used for resin matrix a commercial available material, others developed orthodontic experimental adhesives and then subjected them to tests (2 studies); 27 out of the 28 studies regarding nanoparticles in adhesives were in-vitro studies. As controls, each study used the adhesive (commercial or experimental) without nanoparticles. 7 studies evaluated resin-modified glass ionomer cement enhanced with nanoparticles, the other studies evaluated composites mixed with nanoparticles. The commercial available controls were composites - Transbond XT (21 studies), Enlight Ormco (1 study), Charm Fil-Flow (1 study), Ortho Connect Flow (1 study) - and cements - GC Ortho (3 studies), Vitremer 3M (3 studies), Opal Band Cement Ultradent (1 study).

In the studies evaluated in this review we found as nanomaterials for adhesive enhancement: silica nanofillers, silver nanoparticles, triacryloylhexahydro-1,3,5-triazine, silver benzoate, hydroxyapatite, 2-methacryloyloxyethyl phosphorylcholine, dimethylaminohexadecyl methacrylate, copper oxide, zinc oxide, magnesium oxide, titanium oxide, graphene oxide nanoparticles, fluoride nanoparticles, ionic liquid, curcumin nanoparticles, bioactive glass nanoparticles, chitosan nanoparticles [17-20, 24, 27, 29-44].

The nanoparticles possess reduced dimensions, that allow them more interaction with micro-organisms and represent an advantage of their using as antibacterial material. Streptococcus mutans is one of the main bacteria responsible for caries, therefore many studies evaluated the capacity of new materials of preventing the growth of Streptococcus mutans [36].

In order to increase the clinical applicability of new orthodontic adhesives, an important property of the material is the biocompatibility, therefore further in-vitro and clinical studies are required. Another research direction may be the involvement in the study of a larger variety of teeth, since the majority of investigated tooth structures were premolars/molars. Most frequently, the white spot lesions are encountered on the area of maxillary incisors, particularly lateral maxillary incisors, therefore future clinical studies should evaluate the particularities of these teeth surfaces [1].

Stainless steel brackets are regarded as potential promotors of specific changes in the oral environment, for example they can lower the oral *p*H and increase the plaque formation on their surfaces, therefore the present research aimes to enhance the antimicrobial properties of brackets and wires through coating [45]. According to the studies included in the present review, the bacterial adhesion to orthodontic brackets can be reduced through coating the brackets with titanium oxide and silver nanoparticles [46]. All studies regarding nanoparticles on brackets surfaces were in-vitro researches. Taking into account the specificity of orthodontic treatment, as long-term procedure, we appreciate that it is necessary to evaluate the intraoral effects of coated brackets over a longer period of time and in randomized clinical studies.

Regarding the possibility of archwires coating, our review included a clinical trial aimed to evaluate the effect of titanium dioxide coating on the surface of nickel-titanium archwires and the influence of this procedure on Streptococcus mutans adhesion [48]. The study results proved that the titanium oxide coating is effective in reducing Streptococus mutans concentration. Analysing the mineral content of enamel surrounding the bracket, the authors found week evidence of benefits form the modified archwires.

Another direction for future development of protective orthodontic biomaterials represents the nanoparticles enhancement of elastomeric ligatures. The ligatures, the most common form of orthodontic ligation, are easy to apply, affordable. They are usually made from latex or polyurethane and are replaced at each orthodontic appointment [13]. Their close proximity to the enamel surface could make them ideal and convenient vectors for the delivery of antimicrobials, and for preventing the white spot lesions. According to Kamarudin and coworkers, elastomeric ligatures can be functionalized with chlorhexidine hexametaphosphate through immersion coating and so they can release soluble chlorhexidine continually for more than 8 weeks.

Since 2019, we've noticed an increased interest in developing a wider range of orthodontic biomaterials aimed to protect the teeth enamel. Another strategy for preventing the development of white spot lesions may involve the use of orthodontic sealant prior to bonding orthodontic bracket to enamel, periodic professional check-ups and application of varnishes on teeth surfaces of patients undergoing fixed orthodontic treatment, or regular domestic rinse with a mouthwash containing silver nanoparticles [14, 51, 52]. The existing studies demonstrated that the orthodontic sealants can protect the regions near the orthodontic brackets from acidic attacks caused by bacterial products or acidic attacks of non-bacterial origin. A possible disadvantage of mouthwash use is that the patients' compliance cannot be ideally controlled. We appreciate as beneficial the further development of products aimed to increase the enamel resistance to acid erosion, especially those containing biopolymers like chitosan. Given its capability to decrease the formation of biofilm on teeth surfaces, the chitosan could be considered as a more appropriate alternative over the use of chemical products such as chlorhexidine or fluor ions for orthodontic patients with fixed appliances [6].

4. Conclusions

The present advancement of nanotechnology in the entire field of medicine, and dentistry, in particular, represents a guaranty that orthodontics, a domain of permanent innovations, will benefit from the novel developed biomaterials. Regarding white spot lesions prevention, each major component of the fixed appliance can be enhanced through nanoparticles, since enamel erosions can be prevented by a multifactorial approach. An important aspect of the current research trends is represented by the development of remineralizing agents with nanoparticles that can form a protective layer over enamel and can decrease the biofilm formation.

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