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Literature review

Polymethylmethacrylate/Nanoparticle Composites with Antimicrobial Properties Applied to Dentistry. Systematic Review

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Abstract

Introduction: Polymethylmethacrylate (PMMA) is used in dentistry due to its mechanical, physical and aesthetic characteristics. Thanks to its wide application and increasing need to obtain materials with improved properties, nanoparticles (Nps) are added as an antimicrobial agent or even for biofilm inhibition on oral surfaces. **Objective:** To compare the antimicrobial properties of PMMA/Nps composites in the dental field and thus aid in the prevention of stomatological pathologies. **Material and methods:** A systematic review was conducted out in different databases (*PubMed*, ScienceDirect, *Medline* and *CONRICyT*) to analyse the antimicrobial properties of PMMA with Nps, selected based on inclusion criteria. The review was carried out according to the PRISMA protocol. **Results:** Titanium dioxide nanoparticles ($NpsTiO_2$) showed to be the most studied on a variety of microorganisms. In contrast, silver nanoparticles (NpsAg), showed a higher percentage of bacterial inhibition. During the development of the review, the antimicrobial effect was verified against the most common microorganisms in the oral cavity. The most common microorganisms studied were *Streptococcus mutans* and *Candida albicans*. **Conclusions:** All Nps added to PMMA, either with graphene or individually, have an antimicrobial effect that which has been a constant in recent years due to the advantages they provide.

Keywords: Nanoparticles, polymethylmethacrylate (PMMA), composites, antimicrobial, odontology, properties.

INTRODUCTION

Polymethylmethacrylate (PMMA) is a transparent thermoplastic material traditionally used in the manufacture of dental prostheses[1]. It is a malleable, lightweight, strong, inert radiolucent, non-ferromagnetic and stable material[2]. In addition to these, it possesses mechanical, physical and aesthetic characteristics that differ from other plastic materials, as it has higher translucency, excellent strength, easy mouldability, preserves antagonistic teeth and can be repaired if its surface is scratched; yet its low wear resistance is its main shortcoming[1]. PMMA has also been shown to have a certain tendency to accumulate dental biofilm on appliance surfaces, as well as on hard and soft tissues[3]. This is why in recent decades nanotechnology has been related to dentistry to improve the variety of resin-based materials, including PMMA; this is how nanocomposites emerge that combine a polymer matrix and a nanoscale filler, which provide new properties, both mechanical and physical, which depend on the size and morphology of the Nps[4]. The process for obtaining nanocomposites is carried out by encapsulating nanometric particles, either metallic or metal oxide, in a layer of polymers, giving rise to nanocomposites[5]. In this way, both materials produce a synergy that results in the nanocomposites having better characteristics as a whole than individually[6].

On the other hand, it is known that the oral cavity has many surfaces, from soft tissues to superficial mineralised tissues, each of which is covered by a large number of bacteria generating biofilm on its surface. Some of these bacteria have been considered cariogenic and periodontopathogenic, which are the most common bacterial pathologies in the stomatological cavity in humans[7].

Due to the wide variety of microorganisms that are detected in the mouth, as they are reflected in removable prosthetic materials, orthodontic appliances, resins or any restorative material that is exposed to bacteria, whether Gram-positive or Gram-negative such as streptococci, lactobacilli, enterococci, and even fungi and viruses among a wide variety of other microorganisms, as there are approximately 600 different species in the mouth, but only 1% of them are pathogenic, which are the aetiology of dental caries, gingivitis, periodontitis, stomatitis, odontogenic infections, alveolar osteitis and tonsillitis[8]. Fungal diseases include oral candidiasis[9]. Moreover, we can mention herpes labialis, varicella zoster and Epstein-Barr virus infection as diseases of viral origin[10]. Therefore, it is important to study new materials that inhibit the growth of bacteria, viruses and fungi that can cause dysbiosis in the oral cavity.

Candida albicans is a very common fungus in the mouth, especially in older adults. That is why time, effort and resources are devoted to the search for efficient materials to inhibit its growth, and, given that this sector of the population tends to use different dental prostheses made from PMMA, the scientific community is developing different composite materials that seek to implement antimicrobial and antifungal properties to polymethylmethacrylate, one alternative being the addition of Nps.

This review proposes the analysis of the antimicrobial properties of the Nps that are added to PMMA and thus prevent the proliferation of microorganisms related to the oral cavity. The Nps included in this systematic review are: NpsTiO_2, NpsAg and: Platinum (Pt) Nps, as well as biogenic Nps from *Bacillus amyloliquefaciens* (NpsMAg) and the rhizome of *Curcuma aromatica* (NpsCAg), due to the antimicrobial properties they confer to PMMA. For this reason, a comparison will be made between them, to find out which has a greater antimicrobial effect when added to PMMA, in the dental field and thus help in the prevention of stomatological pathologies.

Due to the antimicrobial effect conferred by the addition of Nps to PMMA, it has been proven that there is a significant reduction of microorganisms such as fungi, bacteria and viruses, which cause infections or pathologies present in daily dental practice. This will help to improve the quality of PMMA in certain conditions of the oral environment. Therefore, the overall objective of the systematic review is to compare the antimicrobial properties of PMMA/Nps composites in the dental field and thus help in the prevention of stomatological pathologies.

MATERIAL AND METHODS

A protocol based on PRISMA[11, 12] guidelines for conducting systematic reviews was developed for the research, which included the following statements:

- **Problem:** the population of interest included the main problems in the use of dental materials, which is the formation of microorganisms that adhere to PMMA, due to poor oral hygiene or the composition of the materials.
- **Intervention:** to carry out a comparative study of the antimicrobial effect conferred by the different types of Nps added to PMMA.
- **Comparison:** the reproduction and development of microorganisms in the oral cavity is reduced with the presence of Nps with antimicrobial properties compared to dental materials lacking them.
- **Results:** the systematic review is expected to obtain significant results in the reduction of microorganisms, thanks to the Nps added to PMMA for various applications in dentistry, as well as comparing the different Nps used for this purpose.

The keywords: nanoparticles, polymethylmethacrylate, composites, antimicrobial, dentistry and properties, were used to perform the literature search, the PICO components of the systematic review are as follows:

PICO components of the literature search

- **Problem:** bacterial proliferation in PMMA prostheses, leading to stomatological pathologies.
- **Intervention:** literature review on composites with different types of Nps to PMMA.
- **Comparison:** carry out a comparative study of the different Nps, doses and Minimum Inhibitory Concentration (MIC).
- **Outcome:** reduction of bacterial growth with a certain type of Nps at a certain concentration.

Articles were included that were no older than six years to date, full text, articles that included in the title: PMMA added with any Nps; to be applied to dentistry; only *in vitro* studies will be included (showing the number of samples taken for each study, type of particle, particle size, organisms inhibited and MIC. Articles published before 2014 were excluded; those applied to an area other than dentistry and articles not related to "PMMA added with Nps".

A first electronic search was carried out in January 2020 by five members, one person in the PubMed database (U.S. National Library of Medicine, National Institutes of Health). Similarly, two individuals in Medline (National Library of Medicine of the United States). Finally, a fifth person in CONRICyT, spanish for Consorcio Nacional de Recursos de Información Científica y Tecnológica (National Consortium of Scientific and Technological Information Resources). The results were subsequently excluded following the criteria, which will be described after the second search.

The second search strategy was carried out again in the same electronic databases in October 2020. On this occasion no articles were added to the review because they did not meet the inclusion criteria that will be mentioned.

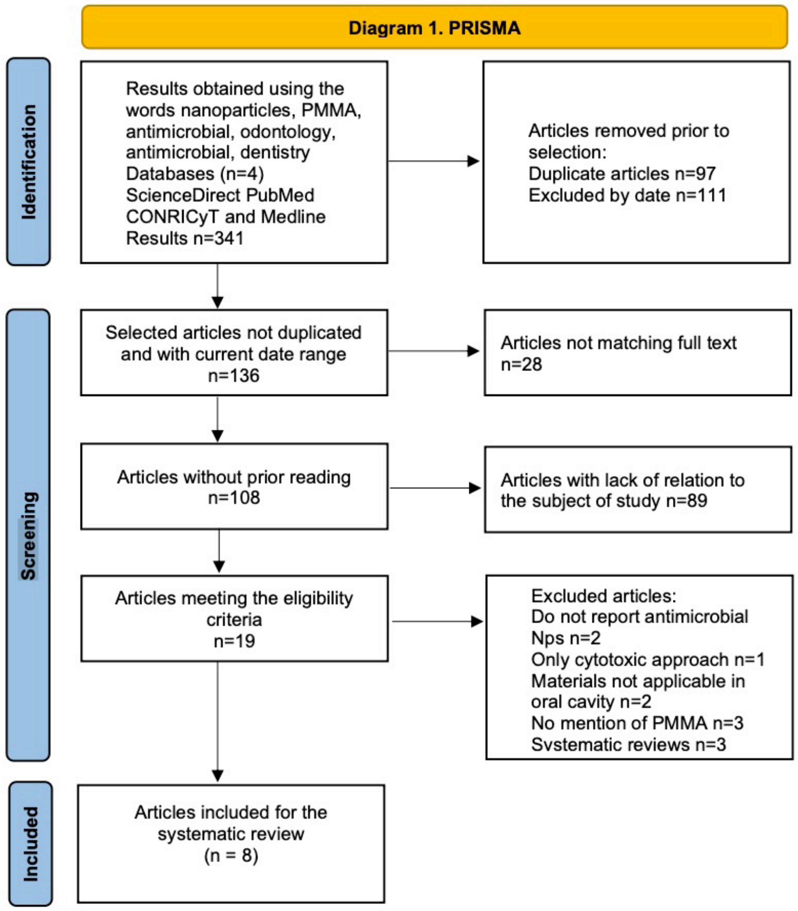
The search strategy chosen was: {Subject AND Adjective} {Subject: (Title) AND Adjective: (Title)}. It was also narrowed down by language and date. The resulting articles were reviewed by five observers to discern which articles met the inclusion criteria based on reading the abstract and title.

RESULTS

The initial search showed 341 studies whose title was related to the search patterns, of which, when duplicates were removed, the result was 247 articles, of which 111 were excluded by the date filter, as they were not systematic reviews, resulting in 136 included articles. When applying a third full-text filter, 108 articles were obtained. After a quick reading of titles and abstracts, 89 were eliminated due to the lack of relation with the topic of study, so only nineteen were included, which provide important information about nanocomposites, therefore, with antimicrobial properties and with application in dentistry. Specifically of those nineteen articles, eleven were excluded as they did not meet the inclusion criteria: two did not report antimicrobial Nps, only mentioning it in the title, one had a clear focus on cytotoxicity rather than antimicrobial effect, two more focused on materials not applicable in the oral cavity and were therefore discarded, three more did not mention PMMA, and therefore met an exclusion criterion, and three of them were literature or systematic reviews. Thus, eight articles were finally selected (Figure 1).

In the second search, 341 articles were obtained, of which 247 were obtained when duplicates were eliminated. When filters were applied, the result was reduced to 136, and when the full text was evaluated and read, eight were obtained again, therefore, the present systematic review is only based on those initially found.

In the eight selected articles, the properties of PMMA/Nps composites of different metal oxides, such as titanium dioxide (TiO_2), silver (Ag), silicon dioxide (SiO_2) and platinum (Pt), were studied[13-20]. One article in the literature even employs graphene Nps to enhance and improve the desired properties of the synthesised composite[18]. Another article studies the possibility of synthesising biogenic silver Nps (NpsAg) from *B. amyloliquefaciens* (NpsMAg) and the *C. aromatica* rhizome (NpsCAg) to reduce the toxicity of chemically synthesised Nps, the latter focused on analysing the effect of biogenic silver Nps in the presence of *Streptococcus mutans*[19].



*Articles related to the topic: "PMMA/NPs composites with antimicrobial properties applied to dentistry" were included.

Figure 1. Diagram PRISMA

Of the articles presented, only four of them were analysed by one-way analysis of variance (ANOVA), which the research relies on to test two or more microorganisms[15-20]. Two of them were also statistically evaluated by means of the Student's t-test[14-20]. One of them was studied ANOVA and Tukey's *post hoc* analysis using SPSS[15] software.

In contrast, the literature presents different methods of MIC study, either by Miles and Misra test, Resazurin-based 96-well plate microdilution method, Kirby-Bauer disk diffusion, Fluorescence-activated cell sorting (FACS) and *Planktonic growth assay* [14, 19-20].

All articles handled different particle sizes, ranging widely from 3-5 nanometres to 170 nm. There is a wide variety of microorganisms inhibited, such as *C. albicans, C. scotti, S. mutans, Lactobacillus acidophilus, Enterococcus faecalis, Pseudomona aeruginosa, S. sobrinus, Staphylococcus aureus* y *Escherichia coli* (Table 1).

Articles were evaluated by the methodological quality scale criteria, using the following guidelines (Table 2)[21]: a) number of samples greater than the mean of 9.6; b) compares inhibitory concentrations; c) choice criteria were specific; d) describes a measure of severity of the treated condition and at least one other measure of the key outcome at baseline; e) specifies

Table 1.
Antimicrobial properties of nanoparticle composites.

Reference	Type of nanoparticles	Number of samples	Particle size (nm)	Microorganisms	Minimal Inhibitory Concentration (CMI)	Results
13	Titanium dioxide (TiO_2)	5	56-170	*C. scotti*	0.4%	Not specified
14	Plata (Ag)	3	20	*C. albicans*	3.5%	94% ± 99% área
15	Titanium dioxide (TiO_2) y silicon dioxide (SiO_2)	6	TiO_2= 21; SiO_2=20	*S. mutans* y *L. acidophilus*	1% for both microorganisms	93% *L. acidophilus* 92% *S. mutans*
16	Titanium dioxide (TiO_2)	24	80-100	*E. faecalis* y *P. aeruginosa*	3% for both microorganisms	92% *P. aeruginosa*
17	Platinum (Pt)	2	3-5	*S. mutans* y *S. sobrinus*	0.1% for both microorganisms	88.9% *S. mutans* y 88.2% *S. sobrinus*
18	silver (Ag) y graphene (G-Ag)	3	NA	*S. aureus, S. mutans* y *E. coli*	2% for all microorganisms	*S. aureus* 90.5* *mutans* 89.0* *y E. coli* 91.67*
19	biogenic silver con *Bacillus amyloliquefaciens* (MAg), y rizoma de *Curcuma aromatica* (CAg)	3	20-40	*S. mutans*	MAgNPs = 3.9µ/mL; CAgNPs = 50µ/mL	MAgNPs=99%; CAgNPs=94%
20.	Titanium dioxide (TiO_2)	18	10-30	*L. acidophilus, S. mutans* y *C. albicans*	2.5% for all microorganisms	Not specified

*Data are presented as mean ± 0.05; T-test was used to calculate statistical significance

the organism(s) on which it acts; f) mentions the optimal antimicrobial inhibitory concentration; and g) inhibits three or more microorganisms.

However, not all of them handle an average number of samples that demonstrate sufficient support to provide reliability, only two of the selected ones do. On the other hand, they do perform an analysis and comparison between the concentrations used to arrive at an MIC, with the exception of two articles, one of which does not specify an MIC in its results, and even among the articles, different techniques were used to evaluate the MIC. Similarly, there are few articles that compare the antimicrobial capacity of more than three microorganisms, only two show this in their results, the rest manage from one to two (Table 2).

DISCUSSION

In the different branches of dentistry, the antimicrobial properties of the different materials used are very relevant and therefore, research has been carried out for years in order to develop materials with better properties. One tool used for this purpose is the addition of various Nps; nonetheless, there is much discussion as to which is the best.

The authors Totu *et al*.[13], Alrahlah *et al*.[16] and Abdulrazzaq *et al*.[20] fabricated PMMA/Nps-TiO_2 nanocomposites at different titanium dioxide (TiO_2) MICs, with the aim of using them

Table 2.
PEDro scale used for the evaluation of the methodological quality of the articles[21]

Article	A	B	C	D	E	F	G
17	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
16	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
14	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**
12	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
18	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
13	**No**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
11	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
15	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

*Data are presented as mean ± 0.05; T-test was used to calculate statistical significance
A) Number of samples greater than the mean of 9.6.
B) Comparison between inhibition concentrations.
C) Choice criteria were specific.
D) Describes a measure of the severity of the condition treated and at least one other measure than the key outcome at baseline.
E) Specifies the target organism(s).
F) Mentions the optimal antimicrobial inhibitory concentration.
G) Inhibits three or more microorganisms.

as denture base, in their studies an evaluation of the antibacterial activity of these composites is performed (table 1). Totu *et al.* evaluated these composites against *C. scotti*, the three composites prepared at 0.4%, 1% and 2.5% $NpsTiO_2$ inhibited bacterial growth, although they did not quantify the level of inhibition at the end[13]. In contrast, Alrahlah *et al.* evaluated PMMA/$NpsTiO_2$ composites with concentrations of 1% and 3% $NpsTiO_2$ against *E. faecalis* and *P. aeruginosa*, resulting in an inhibition of 92%[16]. Furthermore, to evaluating the antibacterial activity, the previous authors also carried out physicochemical characterisation studies and strength tests on dentures moulded from these materials, where they determined that with good distribution in PMMA and in small concentrations, $NpsTiO_2$ can help to improve the mechanical characteristics of PMMA/$NpsTiO_2$ composites, and both authors also agree that the antibacterial effect is enhanced by irradiation under ultraviolet light.

Sodagar *et al.*[15] and Abdulrazzaq *et al.*[20] similarly synthesised PMMA/$NpsTiO_2$ composites, both evaluated against cryogenic bacteria. Sodagar *et. al*. used both $NpsTiO_2$ and $NpsSiO_2$ at 1% against *L. acidophilus* and *S. mutans*, showing results of 93% and 92%[15]. Meanwhile, Abdulrazzaq *et al.*[20] synthesised two PMMA/$NpsTiO_2$ composites at 2.5% and 5% titanium dioxide nanotubes by hydrothermal synthesis and evaluated them against three microbial strains including *C. albicans*, *L. acidophilus* and *S. mutans* under UV irradiation. A decrease of bacterial biofilm on the acrylic resin of the PMMA/$NpsTiO_2$ composite is presented, behaviour that, as the previous authors conclude, intensifies when irradiated under ultraviolet light.

This suggests that $NpsTiO_2$ at concentrations of less than 3% has good antimicrobial activity against *L. acidophilus*, *S. mutans*, *C. albicans*, *E. faecalis*, *P. aeruginosa* and *C. scotti*, and that this antimicrobial activity is enhanced when UV radiation is used. Furthermore, PMMA/$NpsTiO_2$ composites at concentrations below 3% retain and even improve their mechanical and strength properties, and a reduction of cryogenic film is observed on these materials.

With respect to PMMA/NpsAg composites, silver Nps were tested at a concentration of 3.5% against *C. albicans* and showed a surface inhibition range of 94% ± 99%[14]. It should be noted that the preparation of ternary composites, for example PMMA/NpsAg/GO (with graphene), is a viable alternative to lead to materials whose properties can be improved or increased. In this case, these composites were evaluated against *S. aureus*, *S. mutans* y *E. coli*, when evaluated at 2%, better antibacterial activity was observed against *S. aureus* and *S. mutans* than against *E. coli*, with respect to the inhibition halos shown[18]. In contrast, when NpsMAg was evaluated at 3.9µ/Ml, it showed 99% effectiveness against *S. mutans*[19].

The different concentrations and composition show that silver Nps alone are able to significantly decrease the levels of *C. albicans* present on the PMMA surface. But when combined with other materials (composites), the antimicrobial properties of these new materials are considerably increased.

On the other hand, we found that the use of platinum Nps in acrylic discs at 0.1% on S. mutans and S. sobrinus significantly reduced microbial adhesion, to 88.9% and 88.2% respectively[17]. The Gram-positive bacterium S. mutans is the subject of numerous studies, but not all are treated with the same agents, leading to different conclusions.

PMMA/NpsPt composites in general show a good inhibition percentage: 88.9%; but compared to NpsMAg, the latter show a significant difference in inhibition of 99% [17,19]. Compared to PMMA/NpsTiO_2 and SiO_2 composites, the inhibition is 92%, so the use of NpsPt is still relevant.

CONCLUSIONS

PMMA/Nps and PMMA/NpsAg/GO composites were shown to possess an antimicrobial effect on one or more microorganisms. The different Nps are incorporated into PMMA, a dental material essential for the fabrication of dental prostheses. Nps are being extensively investigated in recent years due to their proven advantages in order to develop composite biomaterials with improved properties for dental applications.

In general, the concentration of Nps in the manufacture of PMMA composites plays an important role in the characteristics of the material; at low concentrations (3%) of NpsAg PMMA/NpsTiO_2 or PMMA/NpsPt, the composites tend to retain the mechanical and strength properties necessary for their use in dental prostheses. At concentrations lower than 3% the composites show inhibition in antimicrobial activity, mainly those containing PMMA/NpsAg, and even more so when these are biogenic. Subsequently, PMMA/NpsTiO_2 showed a percentage of inhibition in microbial activity very similar to NpsAg. The NpsTiO_2 are the ones with the most reports and with which a wider range of bacterial inhibition has been observed, and finally there are the platinum ones which, although they show a lower percentage of inhibition, it is still relevant, as this is achieved with the lowest minimum inhibitory concentration. It should be noted that ultraviolet light radiation benefits the antimicrobial effect of PMMA/Nps composites. Not all the articles presented show the percentage of inhibition, but the minimum inhibitory concentration for the reduction of these microorganisms is presented.

Therefore, when comparing the antimicrobial properties of PMMA/Nps composites, the Nps with the best antimicrobial properties are silver Nps, even more so when they are biogenic; however, their effectiveness with a larger number of microorganisms has not yet been investigated. In general, PMMA/NpsAg, PMMA/NpsTiO_2 or PMMA/NpsPt composites ensure an effective reduction of biofilm in dental prostheses made of PMMA, and thus these biomaterials would help in the prevention of stomatological pathologies, without cytotoxic effects, as long as they are used at low concentrations to preserve or improve the mechanical properties of PMMA.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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