UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

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Polimetilmetacrilato modificado por nanopartículas na prevenção da estomatite protética: uma revisão sistemática

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RESUMO

Resinas acrílicas à base de polimetilmetacrilato (PMMA) são materiais amplamente utilizados para confecção de bases protéticas. Entretanto, são propensos à colonização por *Candida albicans*, espécie fúngica comensal e oportunista frequentemente associada ao desenvolvimento da estomatite protética (EP). O potencial antifúngico de resinas acrílicas modificadas por nanopartículas (NPs) tem sido avaliado para a prevenção da EP. Esta dissertação é composta por uma revisão sistemática que teve como objetivo avaliar a eficácia antifúngica do PMMA modificado por NPs. O presente estudo foi conduzido de acordo com o Preferred Reporting Items for Systematic Reviews and Meta-Análises (PRISMA). As buscas foram realizadas no PubMed, SCOPUS, SciELO, EMBASE e LILACS com as palavras-chave “PMMA” OR “denture base” OR “complete denture” AND “nanoparticles” AND “Stomatitis, Denture” OR “*Candida albicans*” OR “biofilm”. Os critérios de elegibilidade foram os recomendados pelo PRISMA. Foram avaliados o tipo de estudo, tipo de NP, método de síntese, método de avaliação antifúngica e efeito antifúngico, os quais apresentaram grande variabilidade. A busca resultou em pesquisas limitadas a estudos in vitro. Entre as NPs estudadas, as mais utilizadas foram aquelas de prata (AgNP) e de óxido de zinco (ZnONP), variando em tamanho de 10 a 100 nm. Outros estudos avaliaram a adição de óxido de cálcio (CaO), dióxido de zircônio (ZrO_2), dióxido de titânio (TiO_2) e prata-vanádio. Métodos mecânicos ou por agitação foram os mais empregados para a incorporação das NPs ao PMMA. Embora todas as NPs terem mostrado atividade antifúngica quando adicionadas ao PMMA, a combinação com o melhor efeito antifúngico foi obtida com ZnONP. Apesar disso, foi observado que a quantidade crescente de NPs implicou na alteração das propriedades intrínsecas do PMMA. Conclui-se que há evidências da potencial ação contra *C. albicans* pelas NPs incorporadas ao PMMA, sendo uma estratégia promissora para prevenir a EP. Entretanto, previamente aos estudos clínicos randomizados, ainda são necessárias pesquisas para a determinação das concentrações inibitórias mínimas para *Candida* spp. bem como para a avaliação da biocompatibilidade desses materiais.

Palavras-chave*: Nanopartículas. Polimetilmetacrilato. *Candida albicans*. Biofilme. Bases de Dentadura.

* Em acordo com os Descritores em Ciências da Saúde (DeCS): http://decs.bvs.br/

ABSTRACT

Nanoparticle-modified PMMA to prevent denture stomatitis: a systematic review

Acrylic resins based on polymethylmethacrylate (PMMA) are materials widely used for denture base fabrication. However, they are prone to colonization by *Candida albicans*, a commensal and opportunistic fungal species frequently associated with the development of denture stomatitis (DS). The antifungal potential of nanoparticle-modified acrylic resins (NPs) has been evaluated for DS prevention. This dissertation is composed of a systematic review that aimed to evaluate the antifungal efficacy of PMMA modified by NPs. The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Searches were performed in PubMed, SCOPUS, SciELO, EMBASE, and LILACS with the keywords “PMMA” OR “denture base” OR “complete denture” AND “nanoparticles” AND “Stomatitis, Denture” OR “*Candida albicans*” OR “biofilm”. The eligibility criteria were those recommended by PRISMA. The type of study, type of NP, synthesis method, antifungal evaluation method, and antifungal effect were evaluated, which showed great variability. The search resulted in investigations limited to *in vitro* studies. Among the NPs studied, the most used were those of silver (AgNP) and zinc oxide (ZnONp), ranging in size from 10 to 100 nm. Other studies evaluated the addition of calcium oxide (CaO), zirconium dioxide (ZrO_2), titanium dioxide (TiO_2) and silver-vanadium. Mechanical or agitated methods were the most used for the incorporation of NPs into PMMA. Although all nanoparticles showed antifungal activity when added to PMMA, the combination with the best antifungal effect was obtained with ZnONP. Despite this, it was observed that the increasing amount of NPs implied in alteration of the intrinsic properties of PMMA. It is concluded that there is evidence of potential action against *C. albicans* by NPs incorporated into PMMA, being a promising strategy to prevent DS. However, prior to randomized clinical trials, research is still needed to determine the minimum inhibitory concentrations for *Candida* spp. as well as for the evaluation of the biocompatibility of these materials.

Keywords*: Nanoparticles. Polymethylmethacrylate. *Candida albicans*. Biofilm. Denture Bases.

*In accordance with Health Sciences Descriptors (DeCS) available at http://decs.bvs.br/

LISTA DE ABREVIATURA E SIGLAS

PMMA	Polimetilmetacrilato
NP	Nanopartícula
EP	Estomatite Protética
Ag	Prata
ZnO	Óxido de Zinco
CaO	Óxido de Cálcio
ZrO_2	Dióxido de Zircônio
TiO_2	Dióxido de Titânio
Ag_2O	Óxido de Prata
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Análises
SciELO	Scientific Electronic Library Online
LILACS	Literatura Latino-americana e do Caribe em Ciências da Saúde

SUMÁRIO

1 Introdução

1 **INTRODUÇÃO**

A candidose oral é a infecção fúngica mais comum entre humanos (AKPAN; MORGAN, 2002; MILLSOP; FAZEL, 2016) e a lesão bucal mais frequente em idosos (RIVERA et al., 2017). A estomatite protética (EP) é a candidose oral de maior ocorrência, sendo relatada em até 88% dos portadores de próteses removíveis (ARENAS-MÁRQUEZ, 2017; AOUN; BERBERI, 2017; BARBEAU et al., 2003; BARNABÉ et al., 2004; FIGUEIRAL et al., 2007; GENDREAU; LOEWY, 2011; GONZÁLEZ-SERRANO et al., 2016; KANSKY et al., 2018; MOOSAZADEH et al., 2016; RAMAGE et al., 2004; RIVERA; DROGUETT; WEBB; SALERNO et al., 2011; THOMAS; WHITTLE, 2005). Essa doença é caracterizada por lesões eritematosas localizadas na mucosa do palato que entra em contato com a base da prótese (NEWTON, 1962; SILVA PINTO *et al*., 2008). Na maioria dos casos, a EP é assintomática, por isso é de difícil percepção pelos pacientes (PERIĆ et al., 2018; PURYER, 2017; TRUHLAR; SHAY; SOHNLE, 1994). Entretanto, quando há manifestação dos sintomas, pode ocorrer desconforto, inchaço, sangramento, prurido, ardor, halitose, gosto desagradável e xerostomia. Além disso, pode haver manifestação de lesões associadas, como queilite angular e glossite romboide mediana (ARENDORF; WALKER, 1987; BUDTZ-JÖRGENSEN, 1974; JEGANATHAN; LIN, 1992; SALERNO et al., 2011).

Embora tenha sua etiologia reconhecida como multifatorial, a infecção por *Candida* tem sido apontada como o principal fator associado à EP, atingindo até 93% dos indivíduos com sinais clínicos de inflamação na mucosa de suporte da prótese (BAENA-MONROY et al., 2005; BANTING; HILL, 2001; MCMULLAN-VOGEL et al., 1999; MUSTAFA et al., 2019; PIRES et al., 2002). Algumas espécies como *Candida glabrata, Candida parapsilosis* e *Candida tropicalis,* podem ser identificadas nos pacientes com essa infecção (MAHDAVI OMRAN et al., 2018; MARCOS-ARIAS et al., 2009; MARTINS et al., 2010; ZOMORODIAN et al., 2011), entretanto a espécie mais comum, *Candida albicans*, é encontrada em 50 a 98% dos casos (ALTARAWNEH et al., 2013; AOUN; BERBERI, 2017; BAENA-MONROY et al., 2005; GENDREAU; LOEWY, 2011; MIMA et al., 2012; MOOSAZADEH et al., 2016; SALERNO et al., 2011; SANITA et al., 2011; SILVA et al., 2012; TAY et al., 2014). Além da infecção por *Candida* spp., múltiplos

fatores etiológicos de ordem local e sistêmica estão envolvidos na estomatite protética. Os fatores sistêmicos incluem antibióticos de amplo espectro (BUDTZ-J.SEN, 1990; DORKO et al., 2001; RITCHIE et al., 1969; SOYSA; SAMARANAYAKE; ELLEPOLA, 2008), imunossupressores, terapias antineoplásicas (GOLECKA et al., 2006), gênero, tabaco, álcool (BARBEAU et al., 2003; SOYSA; ELLEPOLA, 2005), endocrinopatologias (DORKO et al., 2001; GONZÁLEZ-SERRANO et al., 2016), deficiências nutricionais (BUDTZ-J.SEN, 1990; RITCHIE et al., 1969), dieta rica em carboidratos (MARTORI et al., 2014; NIKAWA et al., 1997), debilidade física, alergias, idade (WEERASURIYA; SNAPE, 2008) e comprometimento da resposta imunológica secundário a condições sistêmicas (DOROCKA-BOBKOWSKA et al., 2010; PEREZOUS et al., 2005; SALERNO et al., 2011). Dos fatores locais associados às próteses acrílicas removíveis, destacam-se seu uso ininterrupto, inclusive durante o sono (NEPPELENBROEK et al., 2008), inadequada higiene bucal e das próteses, o trauma local causado pelas próteses antigas e mal adaptadas, com instabilidade oclusal e dimensão vertical reduzida (GENDREAU, LOEWY, 2011), a presença de biofilme protético (PEREIRA-CENCI et al., 2008), a xerostomia (SHIP; PILLEMER; BAUM, 2002) e a alteração do pH da saliva (FIGUEIRAL et al., 2007).

Além dos fatores já mencionados, as resinas acrílicas à base de polimetilmetacrilato (PMMA), embora possuam biocompatibilidade, baixo custo, propriedades mecânicas e estéticas aceitáveis e facilidade de processamento (HASSAN et al. 2019; JADHAV et al. 2018), não possuem eficiência em todos os requisitos físico-mecânicos exigidos para uma prótese dentária, como a previsível formação de microporos e trincas em sua estrutura, favorecendo a colonização por microrganismos patógenos (ALTARAWNEH et al., 2013; da SILVA DANTAS et al., 2016; PEREIRA-CENCI et al., 2007), o que pode levar ao desenvolvimento de infecções locais e sistêmicas (OHSHIMA et al, 2018; WU et al, 2013). Entre esses microrganismos, destacam-se as espécies de *Candida*, que possuem afinidade ao PMMA das bases protéticas devido às suas características hidrofóbicas bem como às propriedades superficiais do substrato tais como rugosidade, energia livre de superfície (ONWUBU et al. 2017) e porosidade (FIGUERÔA et al. 2018). As interações não específicas das espécies de *Candida* com as bases acrílicas são consideradas relevantes na patogênese

da EP (PEREIRA-CENCI et al., 2008; SALERNO et al., 2011). Nessa doença, a capacidade de aderência de *C. albicans* às bases acrílicas é considerada relevante em relação às demais espécies desse gênero (SALERNO et al., 2011). Apesar de 82 filotipos de bactérias serem identificados em biofilmes protéticos, *C. albicans* foi a única espécie fúngica isolada das próteses dos pacientes com EP (CAMPISI et al., 2008). Além disso, quando em formas miceliais, *C. albicans* apresenta uma aderência maior à resina acrílica em relação a outras espécies, facilitando o processo invasivo na mucosa de suporte das próteses (RAMAGE et al., 2004).

Apesar de trincas e microporos favorecer ainda mais a colonização microbiana e, por conseguinte, o desenvolvimento de biofilme, a simples presença de próteses acrílicas removíveis tem sido considerada como um fator predisponente primário para o desenvolvimento da EP (PATTANAIK et al., 2010; ZOMORODIAN et al., 2011). Em indivíduos parcial ou totalmente desdentados, essas próteses podem causar múltiplas alterações no ambiente bucal, tais como variações na saliva e nos depósitos de fosfato, cálcio e proteínas nas superfícies acrílicas de PMMA, que estão em contato com os tecidos de suporte, competição entre microrganismos para aderência ao substrato, diminuição do pH e aumento do potencial de óxido-redução. Como resultado, as espécies de fungos sofrem rápida adaptação osmótica e mudanças metabólicas bem como produzem respostas ao estresse oxidativo, levando à formação de biofilmes (SANCHEZ-VARGAS et al., 2013). A composição da comunidade microbiana do biofilme protético é semelhante à do biofilme dental, com exceção de um aumento de *Candida* spp., em especial *C. albicans*, o que favorece ainda mais tal predisposição à doença (BAENA-MONROY et al., 2005; MARTINS et al., 2016).

Embora seja comprovada a eficácia dos desinfetantes químicos tradicionais para as próteses dentárias, seu uso pode ser prejudicial para os tecidos orais, mesmo em concentrações clinicamente recomendadas (PROCÓPIO et al., 2018), além de resultar em alterações nas propriedades físico-mecânicas dos materiais para base das próteses (POLYZOIS et al., 2013; PARANHOS et al., 2014). Ocasionalmente, a própria limpeza mecânica da prótese pode ser comprometida para alguns pacientes com idade mais avançada ou hospitalizados devido às condições de saúde mental ou física (PAPADIOCHOU; POLYZOIS, 2018). Uma alternativa para esses pacientes é a

utilização de antifúngicos sistêmicos ou locais a fim de reduzir a quantidade de células fúngicas. No entanto, o constante fluxo salivar, a ação de limpeza da musculatura associada e a colonização das bases protéticas por biofilmes complexos acabam por tornar a concentração dos agentes antifúngicos inferior àquela considerada como terapêutica (ALRABIAH et al., 2019). A falha da terapia convencional também tem sido atribuída à falta de adesão ao tratamento, posologia rigorosa da medicação (BARUA et al., 2017) e à resistência microbiana apresentada pelos biofilmes fúngicos, sobretudo de *C. albicans* a agentes antifúngicos e antimicrobianos (NAM, 2014; ROCA et al., 2015). Além disso, é necessário considerar a possível implicação adversa à saúde causada pelos fármacos sintéticos bem como suas interações a outros medicamentos (LOMBARDI; BUDTZ-JORGENSEN, 1993). Tais fatores continuam tornando o tratamento da EP desafiador, sendo observado elevados índices de recorrência em até duas semanas após a suspensão da terapia antifúngica convencional (GENDREAU; LOEWY, 2011; IZUMIDA 2014; NEPPELENBROEK et al., 2008; OHSHIMA et al., 2018; PATTANAIK et al., 2010).

Além de influenciar no tratamento e prevenção de doenças infecciosas da cavidade oral, o aparecimento de cepas resistentes à maioria dos antifúngicos comercialmente disponíveis, bem como novas espécies fúngicas resistentes a múltiplos medicamentos, como *Candida auris*, tem alarmado a comunidade médica, devido à sua alta taxa de mortalidade (até 66% dos casos) (HOKKEN et al, 2019). Em apenas 10 anos de seu descobrimento, *C. auris,* um patógeno nasocomial*,* tem se transformado em um alarmante problema de saúde em pacientes hospitalizados, pela sua característica de “super-hifa” multirresistente a medicamentos (KEAN; RAMAGE, 2019). Por esta razão, torna-se urgente a necessidade do desenvolvimento de novas substâncias antimicrobianas (CASTRO et al, 2015; KEAN; RAMAGE, 2019). Nesse contexto, ao longo dos anos, o PMMA vem sendo modificado por diversos materiais a fim de obter resultados físico-mecânicos mais satisfatórios, bem como maior resistência à colonização microbiana e desenvolvimento de biofilmes, particularmente os de *Candida* spp. (KARAAGACLIOGLU et al., 2007; NAM, 2014; NAWASRAH et al., 2016; REDDING et al, 2009; TSUTSUMI, et al. 2016, VAN DIJCK et al, 2018).

Recentemente, muita atenção tem sido direcionada para a incorporação de nanopartículas (NPs) em PMMA para melhorar suas propriedades. Novos

métodos têm sido desenvolvidos para usinar NPs com forma e tamanho de acordo com o trabalho atribuído. A ideia básica é empregar todos os átomos e moléculas individuais para construir suas estruturas funcionais. Algumas NPs de óxidos metálicos são de natureza iônica e possuem propriedades antimicrobianas, pois possuem grande área superficial com maior número de sítios reativos (STOIMENOV et al., 2002). NPs metálicas e não metálicas, quando combinadas com PMMA e outros polímeros, têm relevância iminente para a função desejada em próteses dentárias, pois apresentam um nível de efeito fungicida mais alto do que os medicamentos antifúngicos convencionais, devido a melhor penetração nas células e tecidos do hospedeiro, mesmo em pequenas concentrações (MONTEIRO et al., 2009).

Algumas NPs de óxidos metálicos, como dióxido de titânio (TiO_2), dióxido de zircônio (ZrO_2), óxido de prata (Ag_2O), óxido de cálcio (CaO), têm comprovado sua ação antimicrobiana devido ao estresse oxidativo incitado por espécies reativas de oxigênio (ROS) (KUMAR, ANTHONY, 2016). As NPs têm maior eficiência na geração de ROS do que seus materiais brutos devido à sua maior área superficial e alta densidade de carga, tornando-as mais ativas no local (LI et al., 2012). Esses nanomateriais têm a capacidade de fixar e penetrar nas paredes celulares de microrganismos Gram-positivos e Gram-negativos por meio de íons reativos (CAO, ZHANG, 2017). Embora a ação antimicrobiana das NPs ainda não seja totalmente compreendida, três mecanismos têm sido sugeridos: (1) reação com peptidoglicano na parede e membrana celular com subsequente morte celular; (2) inibição da síntese proteica; (3) conjugação com DNA bacteriano e obstrução da replicação do DNA (CHEN, HAN, 2017).

Haja vista as considerações anteriores, há uma necessidade de compilar a literatura relevante sobre resinas de PMMA modificadas por NPs para entender a ação antifúngica desses materiais e seus possíveis benefícios clínicos. O desenvolvimento de um novo material, combinando as características do PMMA com os potenciais efeitos antifúngicos trazidos pela nanotecnologia, é de grande importância clínica para a prevenção da DS em pacientes usuários de próteses removíveis acrílicas. Portanto, a presente dissertação teve como objetivo avaliar sistematicamente a literatura com o objetivo de verificar se as NPs poderiam otimizar as propriedades antifúngicas do PMMA.

2 Capítulo 1

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ORIGINAL PAPER

Nanoparticle-modified PMMA to prevent denture stomatitis: a systematic review

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Abstract
This systematic review aimed to evaluate the antifungal effectiveness of polymethylmetacrylate (PMMA) modified by nanoparticles (NPs) and to compare it with conventional acrylic resins for denture bases. The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Searches were performed using PubMed, SCOPUS, SciELO, EMBASE, and LILACS. Eligibility criteria were as recommended by PRISMA. The studies presented great variability regarding NP type, synthesis method, antifungal evaluation method, and antifungal effect. The most commonly used NPs were silver (AgNP) and zinc oxide (ZnONP), ranging in size from 10 to 100 nm. The incorporation methods were mechanical or agitated. Despite PMMA modification by ZnONP being shown in vitro to be a combination with the best antifungal effect, future studies are still needed to determine the minimum inhibitory concentration for *Candida* spp. and assess its biocompatibility before the protocol is clinically tested.

Keywords PMMA · Nanoparticles · Denture Bases · Biofilms · *Candida albicans*

Introduction

Polymethylmethacrylate (PMMA) is widely used in dentistry as a prosthetic material for patients with complete or partial dentures. The advantages of this material include biocompatibility, low cost, acceptable mechanical properties, and ease of processing (Hassan et al. 2019; Jadhav et al. 2018). Despite this, the material has superficial characteristics of hydrophobicity and roughness (Onwubu et al. 2017) related to its porosity (Figuerôa et al. 2018), free surface energy (Pereira-Cenci et al. 2007), and contact angle (Dos Santos et al. 2020), which contribute to microbial adhesion, especially of *Candida* species (Pereira-Cenci et al. 2007; Altarawneh et al. 2013; da Silva Dantas et al. 2016). The adhesion of cells to a substrate is a prerequisite for microbial colonization and formation of a denture biofilm (Ramage et al. 2004; Siddiqi et al. 2018). One of the main consequences of biofilm accumulation on acrylic bases is the development of denture stomatitis (DS), which is considered the most frequent oral lesion in the elderly, with a prevalence of 65% in users of removable acrylic dentures (Figueiral et al. 2007; Gendreau and Loewy 2011). Thus, to prevent DS, it is essential to adopt strategies that reduce adhesion and colonization by *Candida* spp. in PMMA dentures, mainly of *C. albicans*, a species identified in 50 to 98% of acrylic bases of patients with this infection (Baena-Monroy et al. 2005; Figueiral et al. 2007; Gendreau and Loewy 2011; Yarborough et al. 2016; Aoun and Berberi 2017).

Several disinfection protocols for removable acrylic dentures have been suggested to prevent or reduce prosthetic biofilm formation (Valentini-Mioso et al. 2019; Badaró et al. 2020; da Costa et al. 2020). Although effective, the routine use of chemical denture disinfection methods such as immersion in cleaning solutions or physical ones such as microwave irradiation has resulted in deleterious effects on the various properties of PMMA acrylic bases (Pisani

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et al. 2010; Freitas Oliveira Paranhos et al. 2014; Pero et al. 2016; Polychronakis et al. 2018). Moreover, decontamination of denture bases may not be effective in epithelial tissue infected by *Candida* mycelial structures (Kulak et al. 1994; Salonen et al. 1996). Therefore, a number of efforts have been made recently to modify the chemical composition of PMMA or to produce a hydrophilic layer on its surface to prevent biofilm formation (Cierech et al. 2014). In this context, many studies have been conducted to evaluate the antifungal effects of PMMA modification by nanoparticles (NPs) (Monteiro et al. 2011; Nam et al. 2012; Wady et al. 2012; Nam 2014; Suganya et al. 2014; Cierech et al. 2016; De Castro et al. 2016; Li et al. 2016; Anaraki et al. 2017; Anvander et al. 2017; Chen et al. 2017; Gad et al. 2017; Kamonkhantikul et al. 2017; Raj et al. 2018; De Matteis et al. 2019).

Nanometric materials have contributed to advances in the fields of nanomedicine and biomedical sciences because of their excellent physical and chemical properties (Nam 2014; Li et al. 2016). Among the NPs studied, metal oxides stand out for their potential antimicrobial effects (Gu et al. 2007; Yin et al. 2020). This characteristic has been attributed to chemical reactivity as well as to cytoplasmic or microbial surface modifications (Wang et al. 2010; Raghupathi et al. 2011). Thus, there is a need to compile the relevant literature regarding PMMA resins modified by NPs to understand the antifungal action of these materials and their possible clinical benefits. The development of a new material, combining the characteristics of PMMA with the potential antifungal effects brought by nanotechnology, is of great clinical importance for DS prevention in patients using removable acrylic dentures. Therefore, the aim of this systematic review was to answer the question based on the PICOS strategy: could NPs optimize the antifungal properties of modified PMMA compared to conventional PMMA?

Materials and methods

Protocol and registration

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) guidelines (Moher et al. 2009). The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020210202; date of registration: 08/06/2020).

Eligibility criteria and search strategy

Eligibility criteria were defined in relation to PICOS as recommended by PRISMA Statement: Population (P): base dentures (PMMA); intervention (I), NP modifications; comparison (C), conventional PMMA; outcome (O), antifungal properties; and setting (S), in vitro assays. The main objective of this systematic review was to evaluate the antifungal action of NPs added to PMMA for denture bases. In this way, the questions were: (a) Does NP-modified PMMA have antifungal properties that prevent DS? (b) Which NPs are most studied/used for this purpose? (c) Which NP results in the best outcome?

PubMed, SCOPUS, SciELO (Scientific Electronic Library Online), EMBASE (Excerpta Medica Database), and LILACS (Latin American and Caribbean Health Sciences Literature) were systematically searched, considering the key MeSH (Medical Subject Headings) terms for all databases: (PMMA OR "denture base" OR "complete denture") AND ("nanoparticles" OR "reinforcement") AND ("Denture stomatitis" OR "*Candida*" OR "biofilm"). Furthermore, the reference list was reviewed to identify other potentially relevant studies. The last search was conducted on April 6, 2021.

Inclusion criteria included studies in English, published in peer-reviewed journals that addressed in vitro evaluation of NP-modified PMMA for acrylic denture bases. The expected outcome was the identification of an improved antifungal action by these NPs. Duplicate publications and articles that did not correspond to the objectives of systematic review were excluded. As exclusion criteria, studies that did not evaluate PMMA for denture bases and/or addition of NPs and investigations using other types of nanostructures were disregarded. Similarly, publications without a protocol, such as opinion articles, correspondence, editorials, and letters to the editor, were also excluded.

Data extraction and data items

Four researchers (A.A.M.N.G., A.C.G.G., C.Y.C.S., and L.J.A.S.) independently reviewed the titles and abstracts of all identified electronic database citations and determined whether they met the inclusion criteria. Studies that did not meet the inclusion criteria were excluded. Mendeley software (Elsevier) was used to remove duplicate studies. The examiners read the selected articles, and discrepancies between the reviewers were resolved through discussion and arrival at consensus. Reference lists of selected primary articles were also screened to find references that the search strategy did not include, but that would meet the review's eligibility criteria. The results were reviewed by a fifth examiner (K.H.N.).

Data were tabulated in Microsoft Office Excel 2013 and analyzed independently by four reviewers (A.A.M.N.G., A.C.G.G., C.Y.C.S., and L.J.A.S.). The following data were extracted from the included studies: sample size and characteristics, type and size of NP used, amount of NP, antifungal methodology assessed, antifungal outcomes, and additional

information regarding NP characterization, cytotoxicity, and mechanical properties.

Quality appraisal and risk of bias

Evaluation of quality and risk of bias (ROB) was undertaken by two reviewers, with a third reviewer resolving any disagreements. The quality of the articles was assessed using Review Manager 5 software (RevMan, Cochrane). Considering the lack of a defined methodology for in vitro studies, quality was defined by an evaluation of the methodological design of studies, clarity and consistency between results, discussion, and conclusions. The items were categorized as low, unclear, or high ROB.

Results

Scientific information database

A flowchart illustrating the selection of studies for inclusion in the systematic review is presented in Fig. 1. The search process involving all scientific databases led to 161 articles of which, after removing unrelated and duplicate articles, 19 were assessed for eligibility. Finally, 28 articles remained for qualitative analysis.

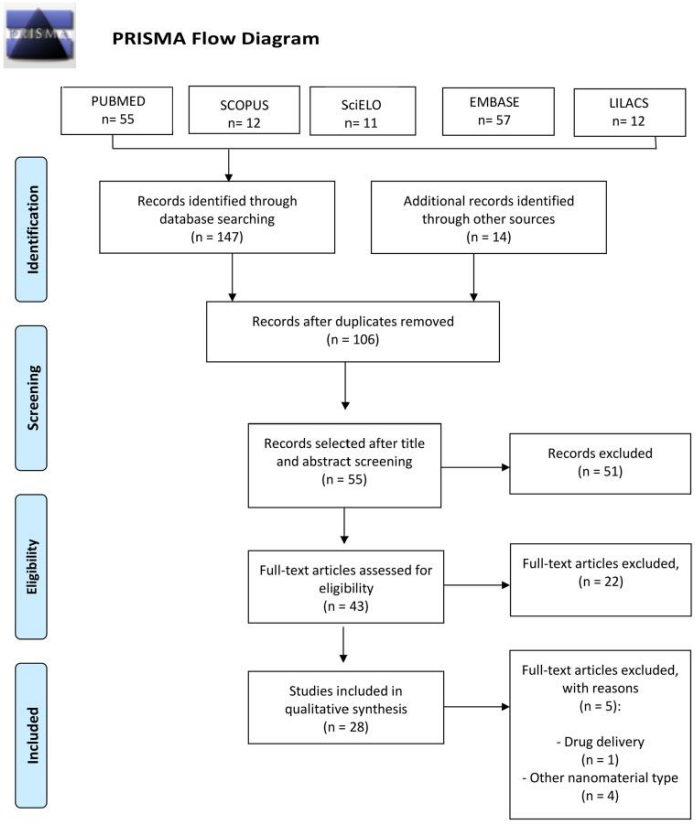

Fig. 1 Selection process of research articles for inclusion in this systematic review

Study characteristics and variability of NPs used for antifungal purposes

Twenty-eight articles were included at the final step of the systematic review. These articles assessed the antifungal properties of denture base PMMA modified by addition of NPs. All selected articles were in vitro studies. Publication dates ranged from 2008 to 2021. All of them used more than one experimental group (varying numbers) and PMMA (self- or heat-cured) as a control group.

Eight studies added silver NPs (Ag pure) (Anaraki et al. 2017; De Matteis et al. 2019; Li et al. 2016; Monteiro et al. 2011; Nam et al. 2012; Suganya et al. 2014; Sun et al, 2021; Wady et al. 2012) and five used zinc oxide (ZnO) (Anaraki et al. 2017; Anwander et al. 2017; Cierech et al. 2016; Kamonkhantikul et al. 2017; Raj et al. 2018). Thus, these were the most commonly employed NPs for the improvement of antifungal effects in denture bases. Other studies assessed the antifungal properties of zirconium dioxide (ZrO_2) (Abualsaud et al. 2021; Gad et al. 2017; Mangal et al. 2019), calcium oxide (CaO) (Anwander et al. 2017), titanium dioxide (TiO_2) (Anwander et al. 2017; Arai et al. 2009; Giti et al. 2021; Totu et al. 2017), silver–zinc zeolite (Casemiro et al. 2008), carboxylated multi-walled carbon nanotubes (Kim et al. 2019), graphene oxide (Lee et al. 2018), copper oxide (CuO) (Giti et al. 2021), cerium oxide (CeO_2) (Park et al. 2021), silica (SiO_2) (Alzayyat et al. 2021), Ag-SiO_2 (Sabouhi et al, 2021), nano-diamonds (Fouda et al. 2019; Mangal et al. 2019) and Ag-vanadate (β-$AgVO_3$) (De Castro et al. 2016), or a combination of various NPs and antimicrobial agents (Chen et al. 2017; Han et al. 2015) (Table 1).

Synthesis of experimental material and specimens

Most previous studies used heat-cured PMMA for the preparation of experimental materials. Only five studies used self-cured PMMA as a comparison group to a heat-cured material (Anwander et al. 2017; De Castro et al. 2016; Kim et al. 2019; Mangal et al. 2019; Park et al. 2021). Studies have generally reported variations in particle sizes between 10 and 100 nm (Table 1).

Table 1 shows that the following mixing procedures were adopted concerning the incorporation methodology: coated, mechanical mixing (mortar and pestle, ball mill, or manually mixed) or by agitation (ultrasonic or vortex). Normally, when the NPs were added to the powder, the blend was mechanically mixed, which is a common condition for adding silver NPs. Nevertheless, when the agitation method was used, the NPs were mixed with the monomer. This condition was observed mostly for ZnONPs.

A variation in the sample size was noted between 5 and 30 specimens. Regarding specimen specifications, there was a lack of standardized methodology among prior studies, diverging not only in shape but also in terms of sample dimensions (Table 1).

Most studies added NPs to PMMA at percentages ranging from 0 to 30 wt%. Only one study added NPs in parts per million (ppm) (Wady et al. 2012), while two others used the ratio form (Suganya et al. 2014; Sun et al. 2021) (Table 1).

Evaluation methods for antifungal activity and effects of NP addition to PMMA

For determination of NP antifungal activity, the method used in 16 of the 28 studies was colony-forming units per milliliter (CFU/mL). Some studies included 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 3′-{1-[(phenylamino)-carbonyl]-3, 4-tetrazolium}bis(4-methoxy-6-nitro)) assays and confocal microscopic analysis. Few studies evaluated the cytotoxicity and/or mechanical, optical, and surface properties resulting from NP addition.

All NPs exhibited antifungal activity, which was greater in proportion to the increase in the number of incorporated NPs. Despite this, it can be highlighted that the intrinsic properties of PMMA change with increasing numbers of NPs (Table 2).

Synthesis of results

Given the considerable heterogeneity of the methodology of the studies, it was not possible to group the results and perform a meta-analysis. To guarantee proper readability, findings from the data were categorized as follows: NP type, incorporation methodology, resin type, number of samples per group, NP size, NP amount, antifungal analysis adopted, main outcomes, and additional data reported in the studies. For absent data, NR (not reported) was used, while information not reported with clarity by the authors was indicated as "unclear" (Tables 1, 2).

Risk of bias within studies

For ROB assessment, RevMan software was employed considering the presence/clarity and critical analysis of the following items: control group, methodological design, material characterization, evaluation method, results, and conclusions. The overall ROB assessment presented a low risk of bias (Figs. 2, 3).

Discussion

Nanotechnologies have been explored as a pharmaceutic tendency to improve antimicrobial characteristics on the molecular and atomic scales (Farokhzad and Langer 2009), including as a strategy to overcome microbial drug resistance

Table 1 Summary of methodological characteristics of the included studies

Study	Nanoparticle (Np)	Incorporation methodology	Material type	*n* (sample size)	Specimens dimension	NP size	Amount incorporated	Antifungal analysis
Abualsaud et al. (2021)	ZrO_2	Mixed with powder and stirred for 30 min	Heat-cured PMMA	5	15 × 2 mm	40 ± 2 nm	2.5%; 5.0%; 7.5%	CFU/mL
Alzayyat et al. (2021)	SiO_2	Blended with the powder at 400 rpm for 30 min	Heat-cured PMMA	10	15 × 2 mm	15 nm	0.05%; 0.25%; 0.5%; 1%	CFU/mL
Anaraki et al. (2017)	ZnO and Ag	Mixed with monomer, homogenized in an ultrasonic set	Heat-cured PMMA	10	4 × 10 mm	10-30 nm (ZnO) 20 nm (Ag)	0.5%; 2.5%; 5%; 10%; 20%	CFU/mL
Anwander et al. (2017)	ZnO CaO TiO_2	Mixed using an overhead shaker	Self-cured PMMA	Unclear	7 × 1.5 mm	ZnO < 100 nm CaO < 160 nm TiO_2 21 nm	0.1%; 0.2%; 0.4%; 0.8%	MTT assay
Arai et al. (2009)	TiO_2	Coating	Heat-cured PMMA	30	10 × 10 × 0.5	NR	NR	ATP SEM
Casemiro et al. (2008)	Silver–zinc zeolite	Added to the power and mixed manually	Heat-cured PMMA	10	8 × 10 × 4	NR	2.5%; 5.0%; 7.5%; 10.0%	Agar plate diffusion method
Chen et al. (2017)	PMMA PMMA + ZrO_2 (2%) + ABWs (4%) PMMA + ZrO_2 (2%) + ABWs (4%) + TiO_2 (3%) PMMA + ZrO_2 (2%) + ABWs (4%) + Ag/TiO_2 (3%) PMMA + ZrO_2 (2%) + ABWs (4%) + Novaron—Silver-supported zirconium phosphate (3%) PMMA + ZrO_2 (2%) + ABWs (4%) + Tetrapod-like zinc oxide whiskers (T-ZnOw) (3%)	Mixed with monomer	Unclear	6	10 × 2 mm	ZrO_2 90 nm ABWs 5–30 µm TiO_2 15–30 nm Ag/TiO_2 30 nm Novaron AG300 0.8 nm T-ZnOw 0.5–5 µm	NR	CFU/mL

Table 1 (continued)

Study	Nanoparticle (Np)	Incorporation methodology	Material type	*n* (sample size)	Specimens dimension	NP size	Amount incorporated	Antifungal analysis
Cierech et al. (2016)	ZnO	Added to monomer, shaked and sonicated	Heat-cured PMMA	Unclear	13 × 13 × 2 mm	NR	2.5%; 5%; 7.5%	Biofilm staining by crystal violet XTT assay Quantitative analysis of adhered *C. albicans*
De Castro et al. (2016)	β-$AgVO_3$	Added to the polymer particle	Heat-cured PMMA Self-cured PMMA	8	9 × 2 mm	NR	0.5%; 1%; 2.5%; 5%; 10%	XTT assay CFU/mL Confocal laser scanning microscopy (live/dead cells)
De Matteis et al. (2019)	Ag	Added to powder and mixed manually	Heat-cured PMMA	Unclear	NR	20 nm	3%; 3.5%	CFU/mL Adhesion by SEM
Fouda et al. (2019)	Nanodiamonds	Added to powder and mixed with mortar and pestle. After, an electric mixer for 30 min at 400 rpm	Heat-cured PMMA	30	10 × 10 × 3 m m	30 nm	0.5%; 1%; 1.5%	Slide count method (Neubauer) CFU/mL
Gad et al. (2017)	ZrO_2	Mixed using a mortar and pestle and stirred for 30 min	Heat-cured PMMA	15	22 × 10 × 2.5 mm	40 nm	2.5%; 5%; 7.5%	*C. albicans* adhesion: Slide count method Direct culture test
Giti et al. (2021)	CuO and TiO_2	Mixed with monomer and stirred by an ultrasonic homogenizer	Heat-cured PMMA	30	10 × 2 mm	17 nm	2.5%; 7.5%	MIC XTT
Han et al. (2015)	PMMA + ZrO_2 (2%) + ABWs (4%) + Novaron	Mixed with the composite by ball milling	Heat-cured PMMA	6	64 × 10 × 3.3 mm	ZrO_2: 50–90 nm, ABW: diameter < 1.5 µm, length 5–30 µm	1%; 2%; 3%; 4%; 5%; 6%	XTT assay CFU/mL
Kamonkhantikulet al. (2017)	ZnO	Homogeneously mixed with liquid monomer using a vortex mixer	Heat-cured PMMA	14	12 × 2 mm	20–40 nm	1.25%; 2.5%; 5% (3 groups + silanized)	CFU/mL
Kim et al. (2019)	Carboxylated multiwalled carbon nanotubes	Added to powder and mixed	Self-cured PMMA	5	11.5 × 1.5 mm	15–20 nm	0.25%; 0.5%; 1%; 2%	SEM Microbial adhesion (PrestoBlue)

Table 1 (continued)

Study	Nanoparticle (Np)	Incorporation methodology	Material type	*n* (sample size)	Specimens dimension	NP size	Amount incorporated	Antifungal analysis
Lee et al. (2018)	Graphene oxide	Added to monomer and sonicated for 1 h	Heat-cured PMMA	5	1.4×3×18	90 nm	0.25%; 0.5%; 1%; 2%	Microbial adhesion (PrestoBlue)
Li et al. (2016)	Ag	Mixed and homogenized in a ball mill	Heat-cured PMMA	9	15×1 mm	NR	1%; 2%; 3%; 5%	Confocal (thickness and dead/live ratios)
Mangal et al. (2019)	Nanodiamonds and ZrO	Added to powder and mixed with mortar and pestle (ZrO) Added to monomer and sonicated at 1000 rpm for 15 min (nanodiamonds)	Self-cured PMMA	NR	10×2 mm	25–50 nm (ZrO) 4–6 nm (nanodiamonds)	0.1%; 0.3%; 0.5% (nanodiamonds) 5% (ZrO)	Microbial adhesion CFU/mL Viability, biofilm quantification
Monteiro et al. (2011)	Ag Colloidal	Added to the monomer	Heat-cured PMMA	5	10×3 mm	NR	0.05%; 0.5%; 5%	CFU/mL
Nam et al. (2012)	Ag	Added to powder and mixed	Heat-cured PMMA	15	20×3 mm	NR	1.0%; 5.0%; 10.0%; 20.0%; 30.0%	CFU/mL
Park et al. (2021)	CeO_2	Added to monomer and sonicated bath-type sonicator for 30 min with ice	Self-cured PMMA	5	11.5×1.5 mm	20 nm	0.25%; 0.5%; 1%; 2%	Microbial adhesion (PrestoBlue)
Raj et al. (2018)	ZnO	Added to monomer and sonicated for 10 min	Heat-cured PMMA	Unclear	12×8×2 mm	60 nm	1%; 2%; 5%; 10%; 15%	CFU/mL
Sabouhi et al. (2021)	Ag-SiO_2	Unclear	Heat-cured PMMA	Unclear	10×10×2.5 mm	20–25 nm	0.1%; 0.3%; 0.5%; 0.7%	CFU/mL
Suganya et al. (2014)	Ag	Added and mixed to the powder	Heat-cured PMMA	10	5×1 mm	20–100 nm	4:1; 3:1; 2:1	Biofilm viability CFU/mL
Sun et al. (2021)	Ag	Added to the powder and mixed Ag solution was mixed with the acrylic acid and then with monomer	NR	6	10×2 mm	40–60 nm	Ag: powder: ratio 1:20 (w:w) Ag solution: acrylic acid at 1:3 (v:v), and then with monomer and powder in a ratio of 3:6:2 (v:v:w)	Bauer–Kirby agar disk diffusion method

Table 1 (continued)

Study	Nanoparticle (Np)	Incorporation methodology	Material type	*n* (sample size)	Specimens dimension	NP size	Amount incorporated	Antifungal analysis
Totu et al. (2017)	TiO_2	Gradually addition of TiO_2 into PMMA solution under continuous stirring followed by ultrasound direct mixing 1 h in a sealed vial	3D printing	Unclear	NR	56–170 nm	0.2%; 0.4%; 0.6%; 1%; 2.5%	MIC Triphenyltetrazolium chloride
Wady et al. (2012)	Ag	Ag solutions were mixed with acrylic powder	Heat-cured PMMA (microwave)	9	13.8×2 mm	NR	30 ppm; 250 ppm; 1000 ppm;750 ppm; 500 ppm	ATP CFU/mL

ABWs aluminum borate whiskers, *Ag* silver, *ATP* adenosine triphosphate, *CaO* calcium oxide, CeO_2 cerium oxide, *CFU* colony-forming unit, *CuO* copper oxide, *MIC* minimum inhibitory concentration, *MTT* (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), *NR* not reported, *PMMA* polymethyl methacrylate, *ppm* parts per million, *SEM* scanning electron microscopy, SiO_2 silicon dioxide, TiO_2 titanium dioxide, *XTT* 3′-{1-[(phenylamino)-carbonyl]-3, 4-tetrazolium}bis(4-methoxy-6-nitro), *ZnO* zinc oxide, ZrO_2 zirconium dioxide, *β-*$AgVO_3$ nanostructured silver vanadate

(Pelgrift and Friedman 2013). In dentistry, nanoscale reinforcing agents have been suggested to improve the mechanical and physical properties of dental ceramics (Pires et al. 2020). In addition, due to the clinical relevance of PMMA in denture composition, modifications to the material using NPs have been proposed (Farokhzad and Langer 2009; Gad and Abualsaud 2019) to prevent acrylic colonization and infections involving supporting tissues.

According to the studies included in the present systematic review, Ag and ZnO were the most commonly added NPs to PMMA. Silver NPs have a larger surface area, resulting in better contact with microorganisms (Rai et al. 2009). This characteristic provides enhanced penetration into the microbial membrane (Li et al. 2016) or attachment to bacterial surfaces based on NP size (Siddiqi et al. 2018). The most likely argument for the growth inhibition mechanism of microorganisms by these nanomaterials is free radical formation (Kim et al. 2007). The release of silver cations from Ag NPs and their penetration causes cell wall rupture, leading to denaturation of proteins and microbial death (Hamouda et al. 2000; Dibrov et al. 2002; Priyadarshini et al. 2013). Results from the study by De Matteis et al. (2019) showed, after 24 h of incubation, the highest decrease of CFU/mL with the addition of 3.5 wt% AgNPs. Furthermore, extending the time of incubation from 24 to 48 h, the reduction of viability was higher.

It has been reported that ZnONPs affect *Candida* cell growth and interfere with their pathogenicity (Jalal et al. 2018). These NPs may exert their effect on the increased induction of anti-oxidative stress in microorganism cells (Cierech et al. 2016). Moreover, there is a significant suppression of hydrolytic proteinases, phospholipases, and activity of enzymes secreted by *Candida* in the presence of ZnONPs. Thus, ZnONPs could be potent inhibitors of hydrolytic enzymes (Jalal et al. 2018). Raj et al. (2018) concluded that uniformly distributed 1 wt% ZnO NPs acted as stress absorbing sites and prevented crack propagation and made the nano-formulations tougher and stronger compared to pure PMMA. A study by Cierech et al. (2016) evidenced the antifungal activity of both PMMA nanocomposites with sprayed solvothermal and hydrothermal ZnONPs and the efficacy of sputtering of ZnONPs on the PMMA layer. The inhibition of fungal biofilm formation as showed by crystal violet assay, improved with increasing concentration of ZnONPs (Cierech et al. 2016).

Although the results for both NPs have shown positive antifungal effects, clinically, there is a need for a set of performance properties for such materials, whether they are mechanical, physical, or biological. The results showed that it is necessary to determine the minimum inhibitory concentrations (MICs) for *C. albicans*, in which the incorporated NPs have no deleterious effects on the properties of PMMA. Although AgNPs have been the main particles used

Table 2 Summary of the results of the included studies

Study	Results	Additional data
Abualsaud et al. (2021)	CFU decreased as the ZrO_2 filler content increased	There was an increase in surface roughness
Alzayyat et al. (2021)	*C. albicans* count decreased with the increase of concentration of SiO_2	The SiO_2 addition results in decrease of the contact angle and translucency, whereas there was an increase in hardness and surface roughness
Anaraki et al. (2017)	Ag NPs exhibited a stronger antifungal effect than ZnO NPs independently of the percentage assessed	Wrinkled specimens with rough and approximately porous surface characteristics were obtained in blank PMMA specimens
Anwander et al. (2017)	Denture base resins with a maximum of 0.8 wt% ZnO, CaO, or TiO_2 nanoparticles are not effective in inhibiting biofilm formation	Rugosity values ranged between 0.04 and 0.07 µm and no significant differences were identified among the various modified denture base resins and the unmodified control. Further studies might, however, address the impact of varying sizes and concentrations of nanoparticles on biofilm formation
Arai et al. (2009)	TiO_2 coating on acrylic resin inhibited biofilm adhesion	There was inhibition for *Streptococcus sanguinis* and *C. albicans*
Casemiro et al. (2008)	The addition of silver–zinc zeolite in all percentages resulted in antimicrobial activity *against C. albicans* and *Streptococcus mutans*	The modification with silver–zinc zeolite modified negatively affected the flexural strength
Chen et al. (2017)	CFU: The 3 wt% additions of various antibacterial agents had significantly antibacterial activities compared to the control and blank groups and the Novaron and T-ZnOw groups had higher antibacterial properties than the other groups	Cytotoxicity: The results revealed that there were no significant differences between all the eluent groups and the negative group after 24 h incubation in the twofold diluted eluents. The undiluted extracts showed TiO_2, Ag/TiO_2 groups were different significantly from other groups. The results showed that antibacterial with 3 wt% Novaron and T-ZnOw in ZrO_2-ABWs/PMMA composites possess substantially higher antibacterial activity, flexural strength, surface hardness and without compromising the cytotoxicity of composites
Cierech et al. (2016)	The antifungal effect increased with increasing concentration of nanoparticles in the composites. Crystal violet: The best results were obtained by 2 types of PMMA samples with coated ZnO NPs; no statistically differences between solvothermal and hydrothermal types were observed	The authors tested a methodology of incorporation of NP into PMMA and another with NP coating
De Castro et al. (2016)	Unclear. *C. albicans* and *S. mutans* biofilms decreased with the addition of β-$AgVO_3$ Concentrations of 5 and 10%: the absorbance values obtained using XTT on *C. albicans* were reduced. In the samples containing 10% additive, almost complete inhibition was observed	For antifungal analysis, the comparison between material types (heat or self-cure) was unclear. For SC, the incorporation of 0.5% β-$AgVO_3$ resulted in a significant increase in surface hardness values. For TR, there was no change. The flexural strength of both resins was reduced when a 2.5% concentration was incorporated, followed by concentrations of 5 and 10% β-$AgVO_3$, but the concentrations of 0.5% and 1% do not change this property. There was no difference in the surface roughness of the acrylic resins when β-$AgVO_3$ was added
De Matteis et al. (2019)	After 24 h of incubation, the CFU/mL decreased with the addition of Ag NPs, and the highest inhibition was observed for a 3.5% concentration of Ag NPs. Extending the time of incubation from 24 to 48 h, the reduction of viability was more evident. After the addition of 3.5% of Ag NPs, the circularity values were reduced from 0.85 ± 0.06 to 0.81 ± 0.08 at 24 and 48 h, respectively	SEM: Topographic images clearly showed a flatter surface when Ag NPs were implemented in PMMA in a dose-dependent manner. AFM: strong reduction of roughness parameter, affecting the colonization and the proliferation of yeast, as confirmed by the Miles and Misra test and SEM analysis. There was a color change: from pink to dark pink/beige
Fouda et al. (2019)	Neubauer and CFU test methods showed decreased in the *C. albicans* count in the nanodiamonds groups compared to control. The modified by 1% and 1.5% had the best microbiology results, without differences between them	Nanodiamond addition to PMMA contributed to decreased surface roughness and not affected the contact angle
Gad et al. (2017)	As the concentration of ZrO_2 increased, the *C. albicans* count significantly decreased. The lowest *Candida* counts were observed with 7.5% zirconia nanoparticles	The authors compared two types of interventions. Samples repaired with modified acrylic resin or intact modified acrylic resin samples

Table 2 (continued)

Study	Results	Additional data
Giti et al. (2021)	7.5% TiO_2 was the only NP with antimicrobial activity against *C. albicans*	Other concentrations of CuO and TiO_2 were effective against *Streptococcus salivarius, Streptococcus sanguis,* and *Candida dubliniensis*. CuO was effective against *S. mutans*
Han et al. (2015)	Both methods (MTT and CFUs) showed reduction of *S. mutans* and *C. albicans* biofilms with Novaron addition	4% of Novaron in ZrO_2–ABW/PMMA offered the best mechanical and antibacterial properties without cytotoxicity
Kamonkhantikul et al. (2017)	Silanized ZnO, particularly with 2.5% silanized ZnO, had a greater antifungal effect	Silanized ZnO (2.5%): fewer color differences, and less opacity, and retaining its mechanical properties
Kim et al. (2019)	There were significant anti-adhesive effects (35 ~ 95%) against *C. albicans, Staphylococcus aureus,* and *S. mutans* for 1% CNT addition in PMMA	It was cytocompatibility of CNT incorporated PMMA in all concentrations of addition. However, mechanical properties (flexural strength and elastic modulus) were gradually compromised with the increase for CNTs incorporated
Lee et al. (2018)	After 1 h of exposure to *Escherichia coli*, *C. albicans*, *S. aureus*, and *S. mutans*, there were significant anti-adhesive effects in graphene oxide-incorporated specimens, which improving with increasing concentrations. Antimicrobial property against *C. albicans* was observed in 2% for up to 28 days	The modification result in no cytotoxicity to oral keratinocytes or change in flexural strength and surface hardness. However, there was an increase in surface roughness and decrease in water contact angle for PMMA with 2% graphene oxide
Li et al. (2016)	Only 5% concentration of Ag NP decreased the biofilm adhesion on acrylic resin. For the biofilm formation assay, the average thickness and the live cell percentage within biofilms that developed on the specimens successively decreased with increasing nano-silver concentration. *C. albicans* could barely form a mature biofilm, on the denture base resin specimens containing 5% silver NP	The low surface roughness of the polished specimens indicated that the polishing procedure for the resin specimens containing nano-silver provided a similar surface that avoided the effect of an irregular surface toward *C. albicans* adhesion
Mangal et al. (2019)	Nanodiamond addition results in reduction in microbial adhesion and viability. Also, there was reduction in salivary biofilm formation compared to the ZrO addition	Nanodiamonds improved the flexural strength, elastic modulus, and surface hardness
Monteiro et al. (2011)	The nanocomposites had good efficacy against *C. albicans*, especially the PMMA/Ag containing 5% silver colloidal NPs	Evaluation: 7, 15, 30, 60, 120 days. Similar flexural strength values between the nanocomposites and the control group were observed. The authors did not find Ag in water immersion (storage), indicating that the method used to incorporate the nanoparticles into the polymeric matrix was effective to retain the nanoparticles
Nam et al. (2012)	The best antifungal effect was shown for 20.0 and 30.0 wt% Ag incorporated, and there were no statistical differences between the two concentrations for clinical use	The MIC of silver cation against *C. albicans* in the present study was revealed to 3.0 mg/l, while the concentrations of eluted Ag + from the modified specimens were 0.176–0.356 mg/l at 24 h and 0.119–0.268 mg/l at 30th day. 20.0 wt% resulted in appropriate physical characteristics through the thermal and EDX analysis when compared to unmodified denture acrylic. However, the improvement of color stability is now required for clinical use
Park et al. (2021)	Decrease in microbial adhesion was observed proportionally to the NP concentration increasing. There was inhibition of adherent *Candida albicans* up to 90%	There was no change in surface roughness, flexural strength and modulus up to 2% cerium oxide. However, in this concentration, surface energy increased and the Vickers hardness decreased
Raj et al. (2018)	Unclear The formulation showed a profound decrease in *C. albicans* colonization compared to the neat polymer at time intervals 0 h, 24 h, 48 h, and 72 h (from 9000 to 1000 CFU)	The addition of ZnO NPs at 1% enhanced the antimicrobial and mechanical behavior of the polymer PMMA without much change in its morphological or structural properties

Table 2 (continued)

Study	Results	Additional data
Sabouhi et al. (2021)	As the $AgSiO_2$ concentration increased, the *C. albicans* counts significantly decreased	$AgSiO_2$ addition also improved flexural strength of specimens
Suganya et al. (2014)	Ag NP showed less *C. albicans* adhesion than the control group after 24 and 48 h incubation period. Ratio 2:1 showed a multifold decrease in the CFUs	NR
Sun et al. (2021)	The modification showed great antimicrobial effects, and could inhibit the proliferation of *C. albicans, E. coli* and *S. mutans* for 14 days of evaluation	Ag solution was mixed with acrylic acid firstly and after with a monomer for the incompatible between them. The color changes to orange-yellow. Bending strength decreased significantly, but they still conformed to ISO requirements. There was no cytotoxicity toward L929 cells, and no sensitizations, such as erythema, edema, ulcer or induration, were observed in animal model. The best results regarding esthetic performance and antimicrobial properties were observed adding Ag to the powder
Totu et al. (2017)	0.4%, 1%, and 2.5% TiO_2 in PMMA inhibited the growth of *Candida scotti*	The modification of 0.4% of TiO_2 to PMMA resulted in homogeneous dispersion of nanoparticles, ensuring the fluidity required for 3D printing
Wady et al. (2012)	Although the Ag NPs solution had antifungal activity, no effect on *C. albicans* adherence and biofilm formation was observed after its incorporation into a denture base resin	Evaluation: 0, 7, 90, 180 days. AgNPs concentrations of 30 ppm or higher, the contact angle values were significantly lower than control, regardless of the storage period. The authors determined previously MIC (3.98 ppm) and minimum fungicidal concentration (15.63) of AgNPs solution against the *C. albicans* in the planktonic state. For sessile (biofilm) cells, a higher value was recorded (MFCs = 1000 ppm)

ABW aluminum borate whiskers, *AFM* atomic force microscopy, *Ag/TiO*$_2$ silver-supported titanium dioxide, *Ag* silver, *CaO* calcium oxide, *CeO*$_2$ cerium oxide, *CFU* colony-forming unit, *CuO* copper oxide, *MIC* minimum inhibitory concentration, *Novaron* silver-supported zirconium phosphate, *NP* nanoparticle, *NR* not reported, *PMMA* polymethyl methacrylate, *ppm* part per million, *SEM* scanning electron microscopy, *SiO*$_2$ silicon dioxide, *TIO*$_2$ titanium dioxide, *T-ZnOw* tetrapod-like zinc oxide whiskers, *XTT* 3'-{1-[(phenylamino)-carbonyl]-3, 4-tetrazolium}bis(4-methoxy-6-nitro), *ZnO* zinc oxide, *ZrO*$_2$ zirconium dioxide, *β-AgVO*$_3$ nanostructured silver vanadate

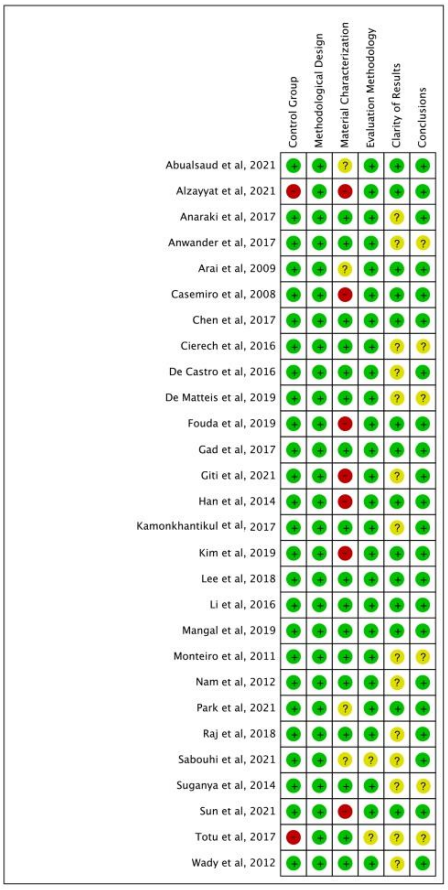

Fig. 2 Risk of Bias summary. Green circles represent a low risk of bias, red circles represent a high risk of bias and yellow circles represent unclear information about selected items (color figure online)

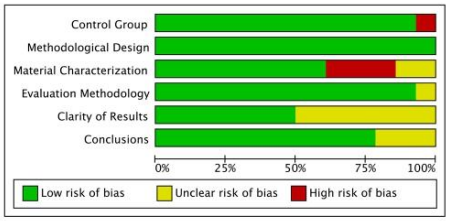

Fig. 3 Risk of bias graph

for antifungal purposes, they were associated with noticeable color changes in PMMA (De Matteis et al. 2019) and a decrease in contact angle (Wady et al. 2012). Moreover, a significant reduction in flexural strength was observed when more than 2.5 wt% Ag-vanadate NPs were incorporated into the experimental materials, and only the addition of 5% silver vanadate NPs resulted in the reduction of *C. albicans* biofilm formation (De Castro et al. 2016). However, when colloidal AgNPs were added to 5 wt%, there was no change in flexural strength (Monteiro et al. 2011). ZnONPs, even at a low concentration (1 wt%), were able to improve the antimicrobial and mechanical behavior of PMMA without detrimentally altering its morphological and structural properties (Raj et al. 2018). In addition, although the 2.5 wt% silanized ZnO resulted in fewer color alterations and less opacity of PMMA, they presented significant antifungal activity, with no deleterious effects on its mechanical properties (Kamonkhantikul et al. 2017).

Another characteristic that leads to an increase in the antimicrobial properties of NPs is their particle size (Siddiqi et al. 2018). The studies included in this systematic review used NPs with sizes ranging from to 10–100 nm. One of the included studies associated silanized NPs with micrometric tetrapod-like zinc oxide whiskers and micrometric aluminum borate whiskers. This discrepancy in particle sizes may have interfered with the obtained results. It is known that antimicrobial efficiency is increased by decreasing NP size because smaller particles attach more easily and penetrate cell membranes more readily (Agnihotri et al. 2014). Although it was not possible to statistically compare the results between the different studies, it is evident that the use of NPs small in size greatly improves the antimicrobial properties of PMMA.

Owing to their antimicrobial properties, NPs can be toxic to humans (Jeevanandam et al. 2018; Sarma et al. 2021). Although it is known that nano-toxicity increases with reducing particle size, the NPs added to the PMMA investigated in the selected studies in the present review displayed no potential cytotoxic effects (Anwander et al. 2017; Chen et al. 2017; Raj et al. 2018; Sun et al. 2021). Despite these favorable results, additional studies are needed to investigate the biocompatibility of NP protocols through histopathological analyses, including at the molecular level.

Among the selected studies, the most commonly used method for assessing antifungal activity of the materials was viable colony counts (UFC/mL). This conventional technique is simple and is based on the count of colonies grown on plates with nutrients, and is considered the gold standard method (Seneviratne et al. 2009; Pereira et al. 2011). Using this methodology, it is possible to estimate the number of

viable microbial cells based on their ability to produce colonies under specific conditions in a given culture medium. It is assumed that each colony counted originated from a single viable microbial cell, and the results are expressed in CFU/mL. A disadvantage associated with this method is that all viable cells are counted, including those with low metabolic activity. For this reason, it would be interesting to have a complementary evaluation using a method that quantifies biofilm metabolic activity, such as XTT assay (Peeters et al. 2008), as adopted in the studies reported by Cierech et al. (2016) and De Castro et al. (2016). Finally, staining with crystal violet can be used to determine the general condition of biofilms, since it allows quantification of the matrix of both living and dead cells constituting the biofilm (Peeters et al. 2008). The XTT assay and crystal violet method were used in only one study (Cierech et al. 2016). Therefore, additional tests are recommended to obtain more accurate results in future antimicrobial analyses.

This study aimed to analyze the antifungal role of NPs when added to PMMA used for denture bases. The present systematic review had certain limitations, as there were no studies involving animal models or clinical trials. The available articles were limited to in vitro studies, thus decreasing the degree of scientific evidence surrounding the subject. Second, comparison of the available results is impaired by the absence of standardization in methodology development. Other limiting factors were the differences in the analyses adopted in the various studies, as well as the dimensions of specimens not specified in international norms. However, considering the importance of the subject, this systematic review was able to compare the most up-to-date literature regarding the antifungal effects of NPs added to PMMA and may contribute important data when designing future clinical trials.

Conclusion and recommendations

There is evidence of the in vitro antimicrobial capacity of NP nanomaterials added to PMMA, which may be considered as a potential strategy to prevent DS. Among the NPs, ZnONPs presented suitable results against *Candida* without compromising the intrinsic properties of PMMA. Nevertheless, it is necessary to conduct additional studies for MIC determination and biocompatibility in vivo before clinical studies involving humans.

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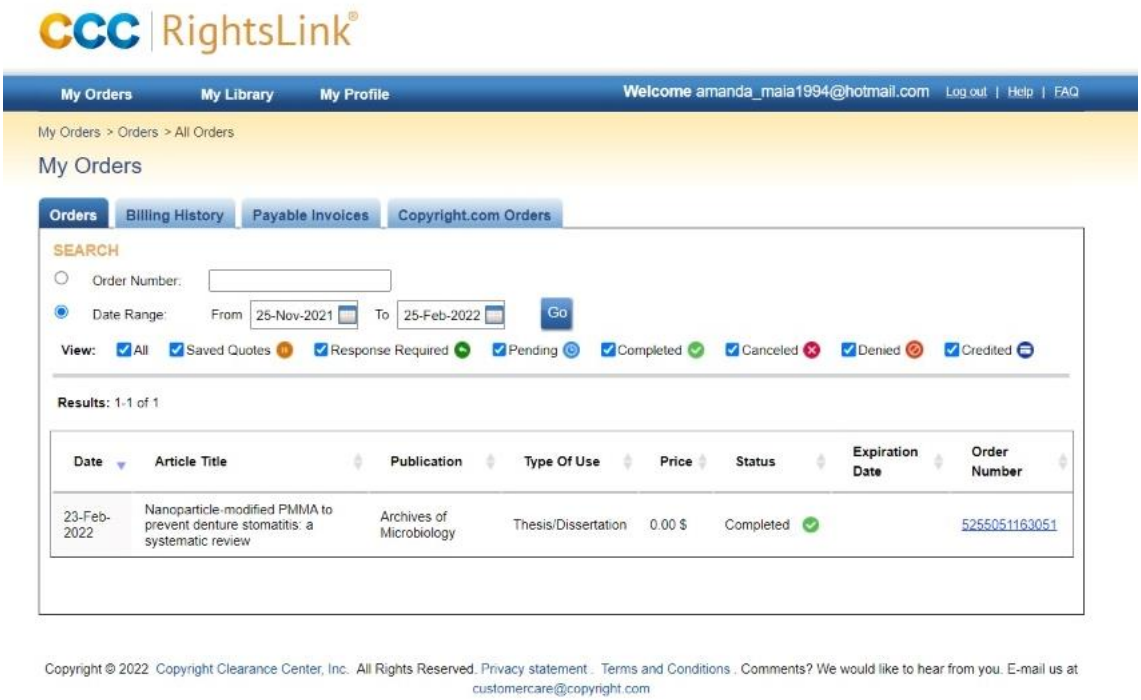
Anexos

Anexo 1

Autorização do periódico para uso do artigo na dissertação



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