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Systematic Review

Effect of the Incorporation of Compounds into Digitally Manufactured Dental Materials—A Systematic Review

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Abstract: The aim of this review was to evaluate if the properties of digitally produced dental acrylic resins improved when reinforced with compounds. A literature search was conducted in PubMed, Web of Science, and Scopus databases for the past 10 years. Combinations of keywords were chosen to reflect the PICO question: Do digitally produced dental acrylic resins loaded with compounds have better mechanical, surface and/or biological properties than resins without compounds? The selection was carried out by two independent researchers according to the PRISMA flowchart and specific eligibility criteria. Results: The 19 in vitro studies included dealt with incorporated compounds such as zirconium dioxide nanoparticles, graphene nanoplatelets, and zwitterionic compounds. It was found that some compounds had a negative impact on the mechanical and surface properties, while others showed improvements. Most of the loaded resins had more effective antimicrobial activity compared to the controls. There were also differences in biocompatibility depending on the type of compound incorporated. The compounds affect the mechanical and surface properties of loaded acrylic resins, depending on the type and concentration of the compound. In the case of antimicrobial activity and biocompatibility, the results depended on other factors than the chemical composition of the compound included in the resin.

Keywords: dental materials; incorporation; CAD-CAM resin; mechanical properties; antimicrobial activity; biocompatibility

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1. Introduction

The geriatric population is increasing due to scientific and technological advances in healthcare, which increase the average life expectancy of the population [1]. Tooth loss is a very common dental problem in this population and has an impact on food swallowing, appearance, and quality of life [2]. Rehabilitation of partial or complete tooth loss can be achieved with a fixed or removable dental prosthesis that improves functional and aesthetic performance [1,3].

Complete dentures for edentulous people were fabricated using conventional methods that involved several clinical and laboratory steps, such as making impressions and plaster models, testing, and selecting the most suitable prosthesis [4]. With the introduction of digital manufacturing technology, the production of prostheses should be optimized and accelerated compared to conventional methods, which means fewer clinical appointments, faster laboratory processes, and less material waste [5].

The use of computer-aided design (CAD) and computer-aided manufacturing (CAM) for the digital fabrication of structures is becoming increasingly common in dentistry, particularly in the fabrication of removable dentures, and this fabrication process involves methods of subtraction and addition [5]. The most common CAD-CAM manufacturing technique in the addition method is rapid prototyping, and in the subtraction method, it is milling. Rapid prototyping uses 3D printing techniques in which the resin is applied layer by layer and then polymerized with various light sources such as visible, ultraviolet and laser light. CAD-CAM milling, on the other hand, is a manufacturing process in which a pre-polymerized resin plate is subtracted [6].

Three-dimensional printing, especially stereolithography (SLA) and the digital light process (DLP), are widely used techniques. SLA is an additive manufacturing technique used for both polymeric and ceramic materials, especially for personalized orthodontic appliances. Compared to the other 3D printing techniques, the SLA process provides better results in terms of surface finish, higher mechanical strength, and greater geometric precision [6]. However, this method also has some disadvantages, as it cannot be sterilized by heat and is a very expensive technology used only for light-cured liquid polymers [7]. The advantages of DLP technology include high precision, smooth surface, fast execution, and lower cost, but it has the same disadvantages as stereolithography [8,9].

Polymethyl methacrylate (PMMA) is a synthetic polymer that is part of most acrylic resins. PMMA has long been used for the fabrication of dentures as it has numerous advantages: Ease of fabrication and repair, good patient acceptance, low cost, biocompatibility, odor and taste neutrality, and good esthetic properties [5]. However, it also has some disadvantages, such as low wear resistance, allergic reactions due to the release of monomers into the oral cavity, and, above all, a high susceptibility to microbial and fungal contamination [4,10–12].

In view of these problems associated with the use of PMMA, the incorporation of compounds into CAD-CAM dental materials is increasingly being investigated to improve the mechanical properties and, above all, to prevent the development of microorganisms. Some examples of compounds with antimicrobial properties are zinc dioxide nanoparticles [13], graphene nanoplatelets [14], silver-reinforced mesoporous silica nanoparticles [15], titanium dioxide [16], cellulose-silver nanocrystals [17], ceramic nitrides [18], zwitterionic materials [19], chlorhexidine [20–24], and tocopherol [25].

In dentistry, new CAD-CAM materials have also been developed that combine the properties of ceramics with those of resins. One example of this type of material is the infiltrated polymeric ceramic network [10]. Examples of other materials currently under investigation are nano-ceramic resins, which consist of 80% zirconia and silica clusters, and lithium disilicate ceramics, which consist of 40% lithium metasilicate crystals [26].

The aim of this systematic review was to analyze whether the compounds incorporated into the acrylic resins produced by CAD-CAM can improve their performance, i.e., surface and mechanical properties; their effectiveness of antimicrobial activity; and to ensure safety through cytotoxicity and genotoxicity tests.

2. Materials and Methods

2.1. PICO Question

A systematic literature search was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [27,28] to answer the following PICO question: Do acrylic resins used in dentistry that are produced using CAD-CAM procedures with incorporated compounds have better mechanical, surface, and/or biological properties than resins without these compounds? (Problem: Acrylic resins produced using the CAD-CAM process; intervention: Incorporation of compounds; comparison: No incorporation of compounds; result: Mechanical and surface properties as well as antimicrobial and biocompatible properties of the resins) (Table S1). The proposal for the study was registered on the National Institute for Health Research, International Prospective Register of Systematic Reviews (PROSPERO) platform with the number CRD42024514141.

2.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were used in this systematic review. The inclusion criteria were articles incorporating compounds in acrylic resins, dealing with CAD-CAM technology in dental medicine, published in the last 10 years, describing in vitro experimental studies, and articles presenting the full version (full text). The exclusion criteria were systematic and narrative reviews; case studies; population studies (case-control and cohort studies); clinical studies; records written in languages other than English or Portuguese; other materials than acrylic resins; not dental materials; grey literature.

2.3. Bibliographical Research

From January to March 2023, a search was conducted in a primary database with MEDLINE, via the search engine PubMed, Web of science and Scopus with the following search equation ("dent*" OR "oral" OR "buccal") AND ("3D" OR "three-dimensional*" OR "print*" OR "CAD-CAM") AND ("acrylic resin" OR "polymethyl methacrylate" OR "poly-methyl methacrylate" OR "PMMA") AND ("incorporate" OR "compound" OR "nano*" OR "particle") AND ("mechanical*" OR toxicity* OR "biological" OR "antibacterial*" OR "antimicrobial" OR "antifungal").

After verification using an EndNote version 21 and exclusion of duplicates articles were assessed by two independent reviewers (CJ, CBN) based on their title and abstract. These reviewers analyzed the titles and abstracts of the selected articles against the inclusion and exclusion criteria. Discussions involving a third reviewer (AB) addressed any disparities in assessments regarding the appropriateness of the study. Subsequently, the full articles and the bibliographic references of each article were analyzed to find relevant articles in this field through a manual search.

2.4. Data Extraction

Extracted data was deposited in an Excel version 2021 sheet and included the characteristics of each study, such as the type of resin, the manufacturing process, the incorporated compound, and the analyzed properties of each study: surface properties, mechanical properties, antimicrobial activity, and biocompatibility.

2.5. Assessment of the Quality of Articles

To assess the quality of the articles that were included in the systematic review, a modified version of the "Guideline for Reporting Pre-clinical In Vitro Studies on Dental Materials" [29] was used. This guideline includes several evaluation items such as: Item 1: abstract, item 2: introduction (2a—background and 2b—objectives), methods (item 3—intervention, item 4—outcomes, item 5—sample size, item 6–9—various types of randomization, item 10—statistical methods), item 11—results, item 12—discussion (limitations), and other information (item 13—financing, item 14—protocols). Then, a total score of 15 points was used to classify each article, depending on the number of positive item assessments, with a score of 0–5 referring to an article with a low overall quality, 6–10 an article with an average overall quality, and a score of 11–15 being considered an article with a high overall quality.

3. Results

3.1. Results of the Bibliographical Research

A PRISMA-FLOW diagram was created to illustrate the results of this systematic review (Figure 1). The results of the bibliographic search in the databases yielded a total of 139 articles: 31 articles from PubMed, 53 articles from Web of Science, and 55 articles from Scopus. After excluding 49 duplicates, 90 articles remained and were evaluated based on their title and abstract according to the inclusion and exclusion criteria. In this phase, 68 articles were excluded: 36 articles did not include compounds, 5 did not mention CAD-CAM techniques, 11 were not acrylic resins, 7 were systematic reviews, 1 was a clinical study, 2 were grey literature, 1 article was written in Mandarin, and 5 articles did not discuss dental materials.

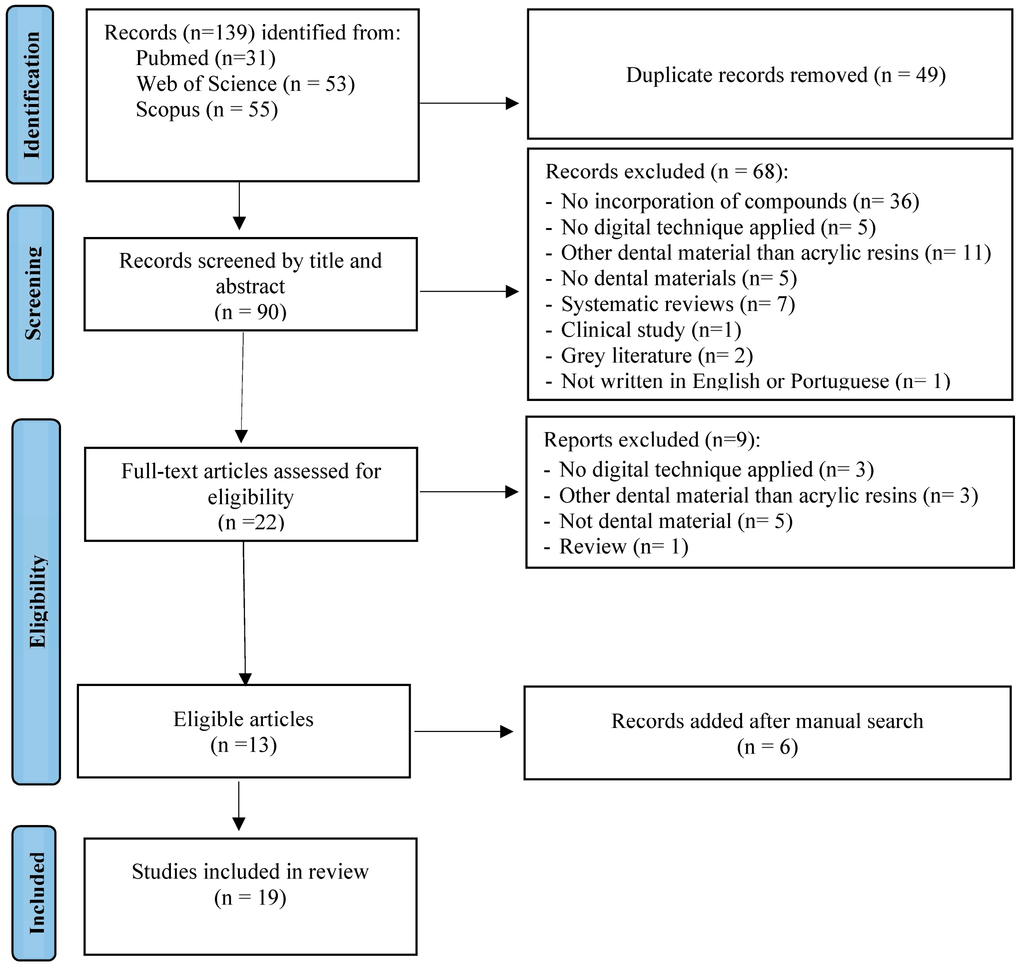

Figure 1. PRISMA-FLOW diagram used for the bibliographic search.

Thus, 22 articles were independently evaluated according to their full-text version to determine whether they met the previously defined criteria. In addition, a search was carried out in the bibliography of the selected articles to analyze which articles could be added manually. Six articles were added through the manual search. A total of 28 articles were analyzed, 9 of which were subsequently excluded because they did not meet the defined criteria. This left a total of 19 articles that could be included in the systematic review for data extraction.

3.2. Main Characteristics of the Studies Included in the Systematic Review

This systematic review includes articles on dental materials fabricated with CAD-CAM whose mechanical and biological properties were possibly modified by the incorporation of composite materials. Thus, 8 articles were analyzed in which the materials were printed using the additive SLA technique, 2 articles referred to fabrication by milling, 8 articles to DLP printing, and 1 article to daylight polymer printing (DPP).

The different compounds incorporated into the CAD-CAM-fabricated dental materials were zirconia nanoparticles (ZrO_2 NPs) [13,30,31], graphene [25], graphene oxide [32], graphene nanoplatelets (GNPs) [14,33], silver-reinforced mesoporous silica nanoparticles (Ag-MSN) [15], aluminum nitride [34], bioactive glasses [35], ceramic nitrides [18], zwitterionic particles [19], nanodiamonds [36], aminated nanodiamonds (A-ND) [37], titanium dioxide (TiO_2) nanoparticles [16,38–40], and silver-reinforced cellulose nanocrystals (Ag-CNCs) [17].

Another piece of information described in most studies is related to the size and distribution of the particles incorporated in the materials. The distribution is often referred to as uniform in the resin matrix [15,31] or forms regular agglomerates [17,37,38,40]. Particle size varied from 4–6 nm of aminated nanodiamonds [37] to 56–170 nm for TiO_2 nanoparticles [40] and 100–150 nm for ZrO_2 NPs [31] (Table 1).

Table 1. Main characteristics of the studies.

Study	Chemical Composition		Manufacturer	Manufacturing Technique	Distribution and Size of Particles	Quality Assessment Score
	Resin	Compound				
Khattar et al., 2023 [13]	PMMA-based resin	Zirconium dioxide nanoparticles (ZrO_2 NPs)	Denture 3D+, NextDent BV, Soesterberg, The Netherlands	SLA printing	Not determined	8 average
Selva-Otaolaurruchi et al., 2023 [32]	PMMA	Graphene oxide	Huge PMMA blocks, Huge Dental Material, Co., Beijing, China	Milling	Not determined	8 average
Salgado et al., 2023 [33]	PMMA-based resin	Graphene nanoplatelets (GNPs) 0%, 0.25%, 0.5%	Dental Sans, Harz Labs, Riga, Latvia	SLA printing	Not determined	8 average
Aati et al., 2022 [14]	PMMA-based resin	Graphene nanoplatelets (GNPs) 0.025%, 0.1%, 0.25%	Denture 3D+, NextDent BV, The Netherlands	DLP printing	Not determined	7 average
Aati et al., 2022 [15]	PMMA-based resin	Silver-reinforced mesoporous silica nanoparticles (Ag-MSN) 0.025%, 0.05%, 0.5%, 1.0%, 2.0%	Denture 3D+, NextDent BV, The Netherlands	DLP printing	Uniform distribution; size 10–20 nm.	7 average
Alshaikh et al., 2022 [30]	PMMA-based resin	Zirconium dioxide nanoparticles (ZrO_2 NPs) 1%, 5%	Denture 3D+, NextDent BV, The Netherlands	DLP printing	Not determined	9 average
Hada et al., 2022 [31]	PMMA-based resin	Zirconium dioxide nanoparticles (ZrO_2 NPs)	Photopolymer resin (Clear V4 resin) (Nagase ChemteX Corporation, Delaware, OH, USA)	SLA printing	Uniform distribution; average size 206 µm; particle size = 100–150 nm.	8 average
Marin et al., 2022 [34]	PMMA-based resin	Aluminum nitride; Barium titanate	Clear photoreactive resin, Formlabs, Somerville, MA, USA	SLA printing	Barium titanate better dispersion than aluminum nitride	6 average
Raszewski et al., 2022 [35]	PMMA-based resin	Bioactive glasses	FotoDent splint, Dreve, Unna, Germany	DPP printing	Not determined	8 average

Table 1. *Cont.*

Study	Chemical Composition		Manufacturer	Manufacturing Technique	Distribution and Size of Particles	Quality Assessment Score
	Resin	Compound				
Marin et al., 2021 [18]	PMMA-based resin	Ceramic nitrides	Clear photoreactive resin, Formlabs, USA	SLA printing	Not determined	4 low
Kwon et al., 2021 [19]	PMMA-based resin	Zwitterionic materials	Orthorigid, NextDent BV, The Netherlands	DLP printing	Not determined	8 average
Mangal et al., 2020 [36]	PMMA-based resin	Nanodiamonds	Orthorigid, NextDent BV, The Netherlands	DLP printing	Not determined	7 average
Mangal et al., 2020 [37]	PMMA-based resin	Aminated nanodiamonds	Orthorigid, NextDent BV, The Netherlands	DLP printing	Particle size 4–6 nm; more agglomerates of nanodiamonds than aminated nanodiamonds	8 average
Mubarak et al., 2020 [38]	Urethane-acrylate resin	Silver-reinforced titanium dioxide nanoparticles (Ag-TNP) 1%, 1.2%	Resin based on urethane-acrylate (Sartomer America, Exton, PA, USA)	SLA printing	Titanium dioxide = 30–40 nm; silver nanoparticles = 5–10 nm	7 average
Agarwalla et al., 2019 [26]	PMMA	Graphene	PMMA, Zotion, Chongqing, China	Milling	Not determined	5 low
Chen et al., 2019 [16]	PMMA-based resin	Titanium dioxide (TiO_2)-polyether ether ketone (PEEK) nanoparticles TiO_2-1%-PEEK-1%, TiO_2-1%-PEEK-2%	Orthorigid, NextDent BV, The Netherlands	DLP printing	TiO_2 nanoparticles = 40 nm; PEEK = 10 µm (irregular)	6 average
Chen et al., 2018 [17]	PMMA-based resin	Silver-reinforced cellulose nanocrystals (Ag-CNCs) 0.05, 0.1%, 0.25%	Denture 3D+, NextDent BV, The Netherlands	DLP printing	Particle size 80 nm, agglomerates due to the high hydroxyl bonding	8 average
Totu et al., 2018 [39]	PMMA-based resin	Titanium dioxide (TiO_2) nanoparticles	E-Dent 100; E-Denture, EnvisionTec GmbH, Gladbeck, Germany	SLA printing	Not determined	5 low
Totu et al., 2017 [40]	PMMA-based resin	Titanium dioxide (TiO_2) nanoparticles	E-Dent 100, EnvisionTec GmbH, Germany	SLA printing	Spherical structure; diameter 56–170 nm	5 low

Legend: PMMA—poly(methylmethacrylate), PEEK—polyether ether ketone; SLA—stereolithography; DLP—digital light processing; DPP—daylight polymer printing.

The studies showed testing of the surface properties (7 articles), mechanical properties (15 articles), antimicrobial properties (11 articles), cytotoxicity (7 articles), and genotoxicity (1 article).

3.3. Surface Properties (Roughness, Topography and Wettability)

Regarding surface roughness, it was found that this parameter depends on the concentration of the compounds. In general, the incorporation of zirconia nanoparticles increased the surface roughness of resins [13,14,30,33], making this effect more evident with increasing concentration [14,33] and subjected them to aging [14,15]. Also, the surface topography changed from flat in the non-loaded resins to having peaks after the incorporation of 0.25% of graphene nanoparticles [14] and 2% of silver-enhanced mesoporous silica nanoparticles (Ag/MSN) [15]. Nevertheless, there were no statistically significant differences in surface roughness between the control group and the groups with nanodiamonds [36] (Table 2).

Table 2. Comparation of outcomes reflecting the relation of incorporated resins with compounds and the control group without compound loading.

Study	Surface Properties	Mechanical Properties	Antimicrobial Properties	Biocompatibility
Khattar et al., 2023 [13] ZrO_2 NPs	Roughness: increased	--------------------	CFU number: decreased	Cell proliferation: increased
Selva-Otaolaurruchi et al., 2023 [32] Graphene oxide	--------------------	Fracture strength: increased	--------------------	--------------------
Salgado et al., 2023 [33] GNPs	Roughness: increased as concentration increased	Hardness: decreased as concentration increased Flexural strength: decreased as concentration increased	--------------------	--------------------
Aati et al., 2022 [14] GNPs	Roughness: increased as concentration increased Topography: control = flat; 0.25% of graphene nanoplatelets = peaks of about 1 µm	Hardness: 0.25% graphene NPs = increased hardness Elastic modulus: decreased as concentration increased Flexural strength: decreased as concentration increased and after aging Fracture strength: decreased as concentration increased and after aging	Adhesion of *C. albicans*: decreased	Biocompatibility: no differences
Aati et al., 2022 [15] Ag/MSN	Roughness: increased as concentration increased Topography: control = flat, Ag/MSN 2% = irregularity	Flexural strength: decreased as concentration increased and after aging Fracture toughness: increased as concentration increased, decreased after aging	*C. albicans* biofilm mass: decreased as concentration increased	FCell viability: increased with 0.025% and 0.05% Ag/MSN, decreased with 1.0% and 2.0% Ag/MSN
Alshaikh et al., 2022 [30] ZrO_2 NPs	Roughness: increased	Hardness: decreased Elastic modulus and flexural strength: dependent on the resin Impact strength: dependent on the resin	--------------------	--------------------

Table 2. *Cont.*

Study	Surface Properties	Mechanical Properties	Antimicrobial Properties	Biocompatibility
Hada et al., 2022 [31] ZrO_2 NPs		Hardness: increased as concentration increased Flexural strength: dependent on the printing direction	--------------------	--------------------
Marin et al., 2022 [34] aluminum nitride, barium titanate	Roughness: increased as concentration increased	--------------------	CFU number: decreased	--------------------
Raszewski et al., 2022 [35] bioactive glasses	--------------------	Flexural strength: decreased	--------------------	Cell viability: 24 h incubation = no differences, 96 h incubation = decreased
Marin et al., 2021 [18] ceramic nitrides	--------------------	--------------------	Antimicrobial activity: increased for *E. coli* and *Staphylococcus epidermidis*	--------------------
Kwon et al., 2021 [19] zwitterionic materials	Wettability: decreased contact angle, with and without aging	Hardness: decreased Elastic modulus and flexural strength: decreased, with and without aging	Bacterial adhesion: decreased for *S. mutans*, *S. aureus*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*	Adsorption of proteins: decreased
Mangal et al., 2020 [36] nanodiamonds	Roughness: no differences	Hardness: increased (18.71 ± 1.25 kg/mm^2) vs. (15.91 ± 1.27 kg/mm^2) Friction coefficient: increased Wear resistance: increased	Bacterial growth: decreased *S. mutans*	--------------------
Mangal et al., 2020 [37] aminated nanodiamonds	Wettability: decreased contact angle	Hardness: increased Flexural strength: increased	--------------------	--------------------
Mubarak et al., 2020 [38] Ag/TNP	--------------------	Hardness: increased as concentration increased Elastic modulus: decreased as concentration increased Flexural strength: increased as concentration increased Tensile strength: increased up to a concentration of 1% Ag; decreased in the group with Ag/TNF-1.2%	--------------------	--------------------
Agarwalla et al., 2019 [26] Graphene	--------------------	Hardness: decreased Flexural Strength: decreased	--------------------	--------------------
Chen et al., 2019 [16] TiO_2-PEEK	--------------------	Flexural Strength: increased Impact Strength: increased	CFU number: decreased in *S. aureus* and *E. coli*	Cytotoxicity (CCK-8 assay): adequate Blood compatibility test: good blood tolerance

Table 2. *Cont.*

Study	Surface Properties	Mechanical Properties	Antimicrobial Properties	Biocompatibility
Chen et al., 2018 [17] CNCs-Ag	--------------------	Flexural Strength: increased but decreased as concentration increased;	Bacterial growth: decreased *S. aureus* and *E. coli*	Cytotoxicity: no differences
Totu et al., 2018 [39] TiO_2 nanoparticles	--------------------	--------------------	Antimicrobial activity: increase for *S. aureus*	Cytotoxicity: no differences DNA damage: no differences
Totu et al., 2017 [40] TiO_2 nanoparticles	--------------------	--------------------	Bacterial and fungi growth: decreased	--------------------

Legend: ZrO_2—zirconia; NPs nanoparticles; CFU-colony-forming units; G—graphene; Ag/MSN—silver-enhanced mesoporous silica nanoparticles; Ag/TNP-titanium dioxide nanoparticles reinforced with silver; TiO_2—titanium dioxide; PEEK—polyether ether ketone; CNCs-Ag—silver-enriched cellulose nanocrystals.

The wettability was assessed by analyzing the contact angle. The contact angle was lower in resins containing nanodiamonds [37] or zwitterionic materials, even after the thermocycling process [19] (Table 2).

3.4. Mechanical Properties

Hardness was evaluated in several articles of the systematic review, and most of the results show that it also depends on the concentration of the compounds. However, when GNPs were incorporated in the resin, one study showed that the groups with higher concentrations (0.25%, 0.5%) showed lower hardness values [33], and another showed that the group with the highest concentration of GNP resin (0.25%) had the highest hardness. After being subjected to an aging process, the hardness of specimens decreased by 6–18% [14]. The addition of zwitterionic materials also decreased the hardness of the resins, even after they were subjected to a thermocycling process. When ZrO_2 NPs were incorporated into NextDent Denture 3D+ and ASIGA DentaBase resins, the resins with this compound showed lower hardness values than the control group [30]. In another study, the group with the highest zirconia concentration was also the one with the highest hardness [31]. For resins containing nanodiamonds, the hardness was higher (18.71 ± 1.25 kg/mm^2) than in the control group (15.91 ± 1.27 kg/mm^2) [36], and the same occurred when aminated nanodiamonds were incorporated [37] (Table 2).

In terms of elastic modulus, the groups with the highest values were the least concentrated resins, and a reduction of about 2–6% was observed after aging [14].

When TiO_2 nanoparticles reinforced with silver were incorporated, the hardness was found to increase with increasing concentration of the compound, except in the group with the highest concentration of nanoparticles in the resins (1.2%), where the hardness decreased [38].

The elastic modulus showed statistically significant differences in the NextDent Denture 3D+ resin group, with the control group showing the highest value (1909.4 ± 679.3 MPa). In the group with ASIGA DentaBase, there were no significant differences in the values, with the group with 5% nanoparticles showing the highest modulus (2031.2 ± 77.2 MPa) [30]. The addition of zwitterionic materials also decreased the elastic modulus [19]. When titanium dioxide nanoparticles reinforced with silver were incorporated, the modulus of elasticity was found to increase with increasing concentrations of the compound [38] (Table 2).

The flexural strength was investigated in several studies. The incorporation of GNPs had a negative effect on this parameter, as the groups with 0.25% and 0.5% had a lower value compared to the control group [26,33]. After 3 months of storage in artificial saliva, all groups showed lower values [14]. When Ag-MSN were incorporated, the flexural strength decreased with increasing silver concentration, and it was also found that all groups showed lower values after 3 months under aging conditions [15]. In the studies on the incorporation of TiO_2-PEEK [17], ZrO_2 NP [30,31], A-ND [37], and Ag-TNP [38], it was found that the group with the highest flexural strength was the more concentrated resin. When bioactive glasses [35], zwitterionic materials [19], or Ag-CNCs [17] were incorporated into acrylic resins, a decrease in flexural strength was observed, even after undergoing the thermocycling process (Table 2).

To compare the fracture strength between the CAD-CAM-fabricated resins with and without graphene oxide, the materials were subjected to several load cycles. It was found that the PMMA + graphene group had better fracture strength values compared to the control group [32]. Another study used GNP, and the group with 0.025% GNP showed the highest value, while the group with the highest GNP concentration showed the lowest fracture strength. After aging, all groups showed lower values [14]. The fracture toughness was also investigated for resins with Ag/MSN, and the higher the concentration of nanoparticles, the higher the fracture strength value compared to the control group [15] (Table 2).

When analyzing the wear rate, the control group showed higher values compared to the other groups, both for stainless steel and titanium, suggesting that the incorporation of these compounds improves wear resistance [36,37] (Table 2).

In the study on the incorporation of zirconia nanoparticles, impact strength was also evaluated, and it was found that the NextDent resin group had higher values compared to the control group, in contrast to the ASIGA resin group, in which all resins with nanoparticles had lower values compared to the control group [30]. This parameter was also examined when using titanium dioxide nanoparticles and PEEK, with the groups with PEEK achieving higher values than the other groups [16] (Table 2).

To complete the evaluation of the mechanical properties in one article, the tensile strength was evaluated in the case of the incorporation of silver reinforced titanium dioxide nanoparticles (Ag-TNP), and it was found that the tensile strength increased up to a concentration of 1% Ag-TNP in the resin. This parameter decreased in the group with Ag-TNF-1.2% [38] (Table 2).

3.5. Antimicrobial Properties

In the studies included in the systematic review, the antimicrobial properties were also analyzed. Most of the dental resins produced with CAD-CAM showed better antimicrobial properties when combined with the investigated compounds. It was found that the incorporation of zirconia nanoparticles [14], aluminum nitride and barium titanate [34], titanium dioxide nanoparticles and PEEK [16], nanodiamonds [36], zwitterionic materials [19], and nitrides [18] into the PMMA resin resulted in a lower number of bacterial colony-forming units (CFU) than the control group. The incorporation of graphene nanoplatelets [14] and Ag-MSN [15] into 3D-printed PMMA resin reduced the adhesion of *Candida albicans* to the resin surface (Table 2).

The incorporation of silver-enriched cellulose nanocrystals [17] and titanium dioxide [39] into the PMMA resin also showed a decrease in the concentration of Staphylococcus aureus bacterial cells, proving that these nanomaterials have an antimicrobial effect.

The titanium dioxide also inhibited the growth of the strain Candida scotti, demonstrating that titanium dioxide nanoparticles have a broad spectrum of activity against Gram-positive and Gram-negative microorganisms and fungi [16,40]. The antimicrobial activity of ceramic nitrides was also investigated in an in vitro test against *E. coli* and *Staphylococcus epidermidis* (Table 2).

3.6. Biocompatibility

Biocompatibility was also assessed in some of the articles selected for this systematic review. Cytotoxicity was assessed in six articles using human oral fibroblasts. Protein adsorption test was investigated in one article [19], the blood compatibility test in one article [16], and genotoxicity [39].

In the case of the incorporation of zirconia nanoparticles (ZrO_2 NPs), the group with the highest cell proliferation was the one with 5% ZrO_2 NPs in the acrylic resin [13]. When graphene nanoplatelets were incorporated, the viability of cells showed no significant differences between the tested groups and the control group [14]. For the Ag/MSN, cell viability was found to be dependent on their concentration in the PMMA resin, as high cell viability was observed in the groups with 0.025% and 0.05% Ag/MSN compared to the other groups [15] (Table 2).

To analyze the effects of the bioactive glasses on PMMA resin, the growth of fibroblasts was examined after 24 h with the PrestoBlue assay and after 96 h with methylthiazolyl diphenyl tetrazolium bromide. It was found that cell viability was not affected after 24 h of incubation, but after 96 h of incubation, cell viability decreased in all groups with bioactive glasses compared to the control group [35]. The adsorption of proteins was also investigated in conjunction with the zwitterionic materials. The analysis of the results showed that the adsorption decreased and was lower in the groups with this compound than in the control group [19] (Table 2).

For the titanium dioxide and PEEK nanoparticles, the cytotoxicity of the groups was analyzed using the CCK-8 assay. This parameter was evaluated for 7 days, and it was found that the groups showed adequate cytocompatibility with these compounds. Blood compatibility was also tested in this study, including hemolysis and analysis of blood coagulation parameters such as activated partial thromboplastin time (APTT) and prothrombin time (PT). The APPT was approx. 36.5 s, and the PT approx. 13.5 s, thus within the normal range. It was concluded that the groups, both the control group and the groups with the nanoparticles, had good blood tolerance [16] (Table 2).

Regarding the incorporation of cellulose nanocrystals reinforced with silver, they show that these exhibit no significant toxicity in L929 fibroblasts compared to the control group. The survival rate of the cells was more than 85% in all groups studied [17]. In the case of titanium dioxide nanoparticles in acrylic resin, cytotoxicity was investigated in two acrylic resins, E-Dent 100 (dent-PMMA) and E-Denture (base-PMMA). In the case of the dent-PMMA material, the extract test was used for the different groups studied (control group, 1% nanoparticles, and 4% nanoparticles), and it was found that the group with the highest viability was the control group, followed by the group with 1% nanoparticles. In the case of the PMMA base matrix, it was evaluated with the XTT method, and there were no differences in the cytotoxic effect between the groups studied [39]. Genotoxicity was evaluated using the micronucleus test (Mtvit) for the two groups, base PMMA without titanium dioxide nanoparticles and base PMMA + 0.4% TiO_2 nanoparticles, and it was found that the TiO_2 nanoparticles caused hardly any DNA damage compared to the negative control group [39] (Table 2).

3.7. Quality Assessment of the Studies

From the 19 included studies, four were considered to have low quality since they scored above six points, and the remaining 15 scored between six and nine points, having average quality (Table 3).

Table 3. Quality assessment of the included studies.

	Items															
Study	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Score**
Khattar et al., 2023 [13]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	yes	no	no	8 average
Selva-Otaolaurr uchi et al., 2023 [32]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	yes	no	no	8 average
Salgado et al., 2023 [33]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	yes	no	no	8 average

Table 3. *Cont.*

	Items															
Study	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Score**
Aati et al., 2022 [14]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	no	no	no	7 average
Aati et al., 2022 [15]	no	yes	yes	yes	yes	no	no	no	no	no	yes	yes	yes	no	no	7 average
Alshaik h et al., 2022 [30]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	yes	yes	no	9 average
Hada et al., 2022 [31]	no	yes	yes	yes	yes	no	no	no	no	no	yes	yes	yes	yes	no	8 average
Marin et al., 2022 [34]	no	yes	no	yes	yes	no	no	no	no	no	yes	yes	no	yes	no	6 average
Raszewsk i et al., 2022 [35]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	no	yes	no	8 average
Marin et al., 2021 [18]	no	yes	no	yes	yes	no	no	no	no	no	yes	no	no	no	no	4 low
Kwon et al., 2021 [19]	no	yes	yes	yes	yes	no	no	no	no	no	yes	yes	yes	yes	no	8 average
Manga l et al., 2020 [36]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	no	no	no	7 average
Manga l et al., 2020 [37]	yes	yes	yes	yes	yes	no	no	no	no	no	yes	yes	no	yes	no	8 average
Mubar ak et al. [38]	yes	yes	yes	yes	yes	no	no	no	no	no	no	no	no	yes	yes	7 average
Chen et al., 2019 [16]	no	yes	yes	yes	yes	no	no	no	no	no	no	no	no	yes	no	5 low
Agarw alla et al. [26]	no	yes	yes	yes	yes	no	no	no	no	no	yes	no	yes	no	no	6 average
Chen et al., 2018 [17]	no	yes	yes	yes	yes	no	no	no	no	no	yes	yes	no	yes	yes	8 average
Totu et al., 2018 [39]	no	yes	yes	yes	yes	no	no	no	no	no	no	yes	no	no	no	5 low
Totu et al. [40]	yes	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no	no	5 low

4. Discussion

In this systematic review, it was found that there are differences in the parameters analyzed depending on the type of compound studied.

4.1. Surface Properties (Roughness, Topography and Wettability)

Regarding surface roughness, it was found that this parameter depends on the concentration of the compound incorporated into the resin. Surface roughness is a parameter that influences both the esthetics and the mechanical properties of the restoration [14]. It has been described that rough materials are more susceptible to the adhesion of microorganisms, which can lead to diseases in the oral cavity such as stomatitis [13,30]. It is influenced by various factors, e.g., the manufacturing method, the type of resin used, and the monomer elution [13]. However, if the surface roughness of the investigated resins is below the recommended limit for dental materials (Sa $\leq$ 0.2 µm), this may not have a major impact on debris accumulation or biofilm adhesion [14]. The compounds incorporated into the resins that showed values below the limit were GNPs [14] and Ag-MSN [15], while in the case of ZrO_2 NPs [13,30] and nanodiamonds [36], the surface roughness values were above the established limit. Although the roughness values are above the limit, the article states that the incorporation of zirconia nanoparticles did not have a major impact on microbial adhesion [13]. The article with the nanodiamonds described that roughness values above 2 µm would increase the possibility of bacterial colonization of the resin surface, which was not observed in the groups studied [36]. It can be concluded that even if the roughness of the tooth material is above the recommended limit, this does not mean that bacterial adhesion will occur. It is necessary to analyze the properties of the individual materials.

4.2. Mechanical Properties

Subsequently, the mechanical properties, antimicrobial activity, and biocompatibility of the resin-containing compounds were analyzed. Some articles describe that the degree of conversion of a resin material is a critical factor because if the polymerization is not performed properly, the mechanical properties and biocompatibility are compromised. The conversion of the polymer monomer is influenced by the layer thickness, the light source, the polymerization method, and the composition of the material [14,15].

The hardness of the material is related to the degree of resistance that a material has to plastic deformation, e.g., due to the abrasive effects that dental material may be subjected to [33], both by medical procedures and by mechanical abrasion during tooth brushing [14]. Dentures made of materials with low hardness can be attacked by tooth brushing, leading to a change in color and the accumulation of bacterial plaque [30]. Therefore, hardness is related to the wear resistance of the prosthesis and is influenced by the composition of the dental material and the polymerization rate [14]. In the case of GNPs incorporated into the Dental Sans resin, there was a decrease in hardness [33], while the incorporation of this compound into the NextDent resin resulted in an increase in hardness the higher the concentration. However, after NextDent resins are aged, their hardness decreases, possibly due to the degradation that occurs [14]. In this way, it can be concluded that this difference in results is due to the different types of resins produced with different manufacturing processes [33]. It has also been reported that the hardness values of 3D-printed resins are lower than those of thermopolymerized PMMA resin, which was also the case when ZrO_2 NPs were incorporated [30]. When zwitterionic materials are added, the hardness also decreases as high doses deteriorate the mechanical properties [19]. PMMA resins with graphene also exhibited lower hardness than the other groups, as some studies have already shown that PMMA-based materials have lower hardness values than other materials investigated in this study [26].

When Ag-TNP were incorporated into urethane acrylate-based resins, the hardness increased with the increase in nanoparticle concentration, except when the concentration was above 1%, as there were problems with printing in this case. When zirconia was incorporated, the hardness increased [31], as did nanodiamonds, which showed a low wear rate compared to the control group [36,37].

The flexural strength of a material is related to the flexibility of the material before it reaches its limit. The bending forces to which the materials are subjected are related to the forces that occur in clinical situations, i.e., the ability of the materials to withstand bending and torsion. Therefore, when dental materials are subjected to permanent deformation, it is important that they have high flexural strength [41]. When analyzing the articles included in this systematic review, it was found that there were differences in the values of this parameter due to the different compounds contained in the resins. In most of the articles, the flexural strength decreased when the compounds were incorporated into the resins.

When graphene nanoplatelets were added, the flexural strength was found to decrease at concentrations above 0.1%. This has also been shown in other articles [33], as when the graphene concentration is above 0.1%, zones of force concentration are created, which affect flexural strength and ultimate strength [14]. Thus, it was described that at lower graphene concentrations, such as 0.01% graphene, the flexural strength of the resin becomes more similar to that of the resin without incorporation [33]. The same occurred when mesoporous silica nanoparticles reinforced with silver were incorporated into the acrylic resin: As the concentration increased, the flexural strength decreased because clusters of these compounds formed in the polymer network. Although the flexural strength of the resin with nanoparticles was impaired, the flexural strength value corresponded to that for dental restorations (ISO 20795-1) [15]. In terms of fracture strength, the resins with this compound showed higher values than the control group, as the nanoparticles impaired the propagation of cracks and fissures in the resin [15].

In the case of zwitterionic materials in resins, some studies have already reported that their high dose in dental materials may negatively affect the mechanical properties, which is related to the gelation process of zwitterionic materials in high concentrations, which affects the polymerization process of the resin. However, it is important to note that the results presented in this article are in accordance with ISO 20795-1 [19]. For the zirconia nanoparticles (ZrO_2-NP), the increase in flexural strength in the ASIGA resins depends on the concentration of ZrO_2-NP, as this parameter also increases with increasing concentration [42]. In the NextDent resins, however, the flexural strength is higher in the group with 1% ZrO_2-NP, while it decreases in the other groups, so that the difference in the flexural strength values could be due to the different compositions of the resins tested. This article also described that the 3D-printed resins fulfill the ISO recommendations (65 MPa) as the minimum value for the flexural strength of this type of material [30]. When zirconia was incorporated into the resin, the printing direction affected the flexural strength values, as in the 0° printing direction, the control group showed a higher flexural strength, while in the 90° printing direction, the group with 3% zirconia showed the highest value. This study showed that the flexural strength value of the resin with 3% zirconia printed at 90° was in line with the ISO10477 recommendation [31]. The introduction of bioactive glasses reduces flexural strength and fracture resistance [35].

When aminated nanodiamonds were incorporated into the resin, their incorporation was found to increase flexural strength, as it has already been described in several studies that their addition increases mechanical strength due to their strong covalent bonds and the fact that they are evenly distributed in the polymer [37]. When investigating the incorporation of graphene into PMMA resins, it was found that nano-ceramic resins (LU) and lithium disilicate ceramics (EX) had higher flexural strength values than the other materials, namely polyurethane resins. PMMA, which contained graphene. In the LU group, the higher flexural strength was due to the formation of zirconia/silica agglomerates; in the EX group, the high flexural strength was related to the homogeneity of the crystals in the ceramic. It was also described that further clinical studies on flexural strength after the incorporation of graphene into PMMA resins are needed [26].

Finally, the flexural strength of titanium dioxide and PEEK nanoparticles and silver-reinforced titanium dioxide nanoparticles in acrylic resins was also investigated. For the silver-reinforced titanium dioxide nanoparticles, the flexural strength was only impaired when the concentration of this compound was greater than 1% because agglomerates formed, resulting in poor dispersion of this compound in the resin matrix [38]. In the case of titanium dioxide and PEEK nanoparticles, their incorporation into the PMMA resin leads to an increase in flexural strength compared to the control group. However, in group 2 (TiO_2-1%-PEEK-0%), problems occurred during the printing process as agglomerates of TiO_2 nanoparticles formed, especially in the polymerization phase of the resin, which affected the flexural strength value and impaired the polymerization phase of the resin [13]. It was also reported that the incorporation of PEEK reduced the agglomeration of the nanoparticles and thus improved mechanical properties [16]. When cellulose nanocrystals reinforced with silver were incorporated, it was found that their concentration was a critical factor because, although the nanocrystals were well incorporated into the resin matrix, their agglomeration on the surface could affect the flexural strength [17].

The accidental fall of dentures is one of the most common causes of fractures. It is therefore important that dental materials have good impact resistance [30]. The impact strength of resins with zirconia nanoparticles has increased because they are evenly distributed in the acrylic resin matrix. However, as with flexural strength, there were also differences in impact strength between the two resin types. The NextDent resin showed an increase in impact strength, while the ASIGA resin did not, which could be related to the printing process [30].

When titanium dioxide and PEEK nanoparticles were incorporated into the resins, it was found that the groups with higher concentrations of these compounds achieved higher impact strength values than the control group. These results could be related to the fact that the compounds incorporated into the resin matrix are able to absorb large amounts of fracture force and prevent the absorption of energy through the destructive cracks present in the material. However, to observe this behavior, it is important that the nanoparticles do not aggregate in the polymer matrix [16]. When graphene oxide was incorporated into PMMA acrylic resin, it was found that the fracture strength in these groups was improved by the compound compared to the control group. The good homogenization of graphene oxide in the acrylic resin influenced this parameter, and the study described that this compound has good properties for incorporation into dental and orthopedic prostheses [32].

Friction and wear resistance has been studied in the incorporation of nanodiamonds [36,37] and is a parameter that must be considered in dental materials, as wear and friction in the oral cavity depend on several factors, e.g., the wetting properties of saliva and the concentration of salivary proteins [36].

Tensile strength is a parameter often used to measure the ductility of a material [40,41]. When Ag-TNP were incorporated into the acrylic resin, an increase in tensile strength was observed, except at a concentration of 1.2% [38].

4.3. Antimicrobial Properties and Biocompatibility

Finally, antimicrobial activity and biocompatibility were also examined as parameters in this systematic review. The biocompatibility of dental materials is a factor that must be considered in their manufacture, as it is important to avoid adverse reactions during treatment. The toxicity of acrylate-based resins is related to the possibility of unpolymerized monomers migrating and subsequently penetrating the oral cavity [15]. Therefore, it is important that this polymerization process of acrylate resins be carried out completely. It is also important to wash the dental materials in alcoholic solutions to remove unpolymerized monomers [35].

Regarding zirconia nanoparticles in resins, it has been described that their antimicrobial effect is related to the production of reactive oxygen species that inhibit the activity of microorganisms by forming pores in the cell wall, which increases cell permeability and causes cell death [13]. This article also described that the incorporation of zirconia nanoparticles, the type of resin, and the hydrophobicity of the resin affect the adhesion of *C. albicans* [13]. Regarding cell proliferation, it has been described that the cell counting method (CCK-8/WST-8) is a reliable, accurate, and practical method to determine the amount of biofilm for the studied microorganisms [13].

Several mechanisms involved in the inhibition of antimicrobial activity have been identified in the context of graphene nanoplatelet incorporation. In terms of physical damage to the microorganisms [14,15], the graphene nanoplatelets rupture the cell membrane and cause cell death. Another proposed mechanism is the entrapment of microorganisms in the graphene layers, preventing cell nutrition. Finally, it has been described that the antifungal effect of graphene is due to the formation of oxygen radicals, which increase cytotoxicity. However, in vitro studies investigating the viability of the oral biofilm revealed that no toxicity occurred in oral cells, possibly due to the low concentration of incorporated graphene nanoparticles as well as the presence of the polycarboxylate functional group, which improves the biocompatibility of graphene [14].

With respect to silver-enriched mesoporous silica nanoparticles (Ag/MSN), it has been described that the toxicity of silver is related to the release of large amounts of ions that ultimately affect the release of oxygen radicals. Therefore, it is important to incorporate silver into mesoporous silica nanoparticles to reduce their toxicity. In this case, it was found that the cell viability of the groups with 1–2% Ag/MSN decreased compared to the others, possibly due to the release of monomers by the resin and silver ions. However, all species achieved a cell viability of greater than 75%, which is not considered a toxic effect according to ISO 10993-5 [15]. Regarding the mechanism of antimicrobial activity of Ag/MSN, it was mentioned that the amine group shows antimicrobial activity due to the interaction between the positive charge of the amine group and the negative charge of the cell membranes of the microorganisms. On the other hand, the amine group increases the hydrophobicity of the surface, which ultimately prevents the adhesion of microorganisms. The penetration of silver ions also leads to cell death because the cell membranes rupture [15].

For the ceramic nitrides Si3N4, Hf3N4, Zr3N4, and AIN contained in acrylic resins, the antibacterial activity of silicon and aluminum nitrides has been associated with the release of ammonia at the surface, while the mechanism for hafnium and zirconium nitrides has not yet been described, as further studies are needed to understand the mechanism of their antimicrobial activity [18]. The zwitterionic materials in the resins have a similar morphology to the lipid bilayers of cell membranes, with a hydrophilic head and a hydrophobic tail. When resins containing zwitterionic substances are exposed to the oral environment, they repel the proteins in human saliva through their interaction with water molecules, thus preventing the adhesion of microorganisms in the oral cavity. It has been described that groups of zwitterionic substances have the ability to inhibit bacterial adhesion even after being exposed to hydrothermal fatigue through a thermocycling process, but it is not clear which mechanism of action causes the antimicrobial activity [19].

Regarding the nanodiamonds investigated, it was found that surface hydrophobicity is a parameter that influences the formation of biofilms on dental materials. Due to their antimicrobial activity and the high hydrophobicity of acrylic resins with nanodiamonds and nanodiamond aminates, these materials are able to resist the formation of biofilms and thus exhibit high antimicrobial activity [36]. The incorporation of zirconia and PEEK nanoparticles into PMMA resins does not alter cytocompatibility, as shown by the analysis of L929 fibroblast survival rates and blood compatibility. Several studies have already mentioned that dental materials can damage the cellular integrity of red blood cells if they have a hemolysis rate greater than 20%. The APTT is a sensitive test for the coagulation system, while the PT refers to hemostasis, with acceptable values ranging between 27–40 s and 11–14 s. In this case, it was found that all groups had values within the acceptable range, showing that zirconia and PEEK nanoparticles have good blood compatibility [16].

Regarding the cellulose nanocrystals reinforced with silver, the article did not describe the mechanism of action, but only what is described in the results [17]. Therefore, further studies are needed to analyze the mechanism of action of nanocrystals that exhibit antimicrobial activity and biocompatibility. [43] Finally, the titanium dioxide nanoparticles incorporated into the resins also have an antimicrobial effect by deactivating the cellular enzymes, which leads to the disintegration of the cell wall and thus to cell death. The article also states that a concentration of 0.4% titanium dioxide nanoparticles prevents the colonization of microorganisms [39,40]. Preliminary studies on cytotoxicity and genotoxicity tests have shown that a concentration of 0.4% titanium dioxide nanoparticles shows positive results when this compound is incorporated into acrylic resins [39].

5. Conclusions

In this systematic review, the surface properties of acrylic resins with incorporated compounds were analyzed, and it was found that the concentration of the compound incorporated into the acrylic resin and the manufacturing process influence this parameter. It was also described that there is a threshold value for the roughness of dental materials and that some of the investigated compounds have higher roughness values. However, further studies are needed to determine whether this parameter can also be influenced by the physiological conditions in the mouth, such as pH, as the selected articles, which are only in vitro studies, are not exposed to the same loading conditions as in the oral cavity.

In terms of mechanical properties, the results showed that there is a wide range of results depending on the different compounds contained in the resins, as there are several factors that influence the determination of these parameters. Therefore, it was concluded that there is no significant scientific evidence that all compounds contained in acrylic resins improve mechanical properties compared to control groups. The studies analyzed in this systematic review have some limitations, as only in vitro studies were analyzed. For future work, it is suggested that more studies be conducted, including studies that adequately evaluate the mechanical properties of dental materials under mechanical and thermal loading conditions such as those in the oral cavity, using different concentrations of nanomaterials, different resins, and different manufacturing techniques with CAD-CAM. Some articles also pointed out the need to conduct long-term studies to analyze the properties of dental materials in a clinical environment.

Finally, regarding the antimicrobial activity of the resins with the incorporated compounds, an improvement in antimicrobial activity was observed compared to the control group. In terms of biocompatibility, not all resins containing compounds were found to have better biocompatibility than resins without compounds. One of the limitations in the articles used for the systematic review was the fact that the groups studied were not exposed to the pH conditions characteristic of the oral cavity, and this parameter has an influence on bacterial adhesion. Therefore, in order to make a clearer statement about antimicrobial activity and biocompatibility, more studies need to be conducted in which resins with and without compounds are exposed to intraoral conditions, and longitudinal studies need to be conducted to determine whether the incorporation of these compounds into acrylic resins actually has an impact on clinical practice.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app14072931/s1, Table S1: PRISMA 2020 checklist.

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