



Biocompatibility of 3D-Printed versus Conventional (Acrylic and Bis-Acrylic) and CAD/CAM-Milled Resins for Provisional Fixed Prosthetic Restorations: A Systematic Review

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How to cite this paper: Baldé, S., El M'Daghri, M., Solié, V. and Amine, M. (2026) Biocompatibility of 3D-Printed versus Conventional (Acrylic and Bis-Acrylic) and CAD/CAM-Milled Resins for Provisional Fixed Prosthetic Restorations: A Systematic Review. *Open Access Library Journal*, 13: e15621.

<https://doi.org/10.4236/oalib.1115621>

Received: June 13, 2026

Accepted: July 7, 2026

Published: July 10, 2026

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Abstract

Background: 3D-printed resins are increasingly used for temporary restorations in fixed prosthodontics, but their biocompatibility compared to conventional and CAD/CAM-milled resins remains insufficiently established. **Objectives:** To synthesize data on the biocompatibility of 3D-printed temporary resins compared to conventional and CAD/CAM-milled resins, and to identify post-processing parameters influencing this profile. **Sources and Methods:** The protocol was registered on PROSPERO (CRD420261383298). The systematic review was conducted according to PRISMA 2020 guidelines in PubMed, Scopus, Web of Science, and OpenAlex for the period 2015-2026. *In vitro* and *in vivo* studies reporting at least one quantitative biological endpoint (cell viability, monomer elution, degree of conversion) and including a conventional or CAD/CAM comparator were included. Risk of bias was assessed using QUIN (*in vitro* studies) and RoB 2.0 (RCTs) by two independent reviewers. **Results:** Thirteen studies included (12 *in vitro*, 1 RCT); moderate risk of bias for 11 *in vitro* studies, low risk for the RCT and 1 *in vitro* study. Cytotoxicity is product-specific; post-polymerization < 15 min induces a reduction in cellular metabolism, whereas 15 - 20 min results in a profile comparable to that of milled resins. Monomer elution is higher for printed resins (53 - 87 $\mu\text{mol/L}$) than for milled blocks (7.6 $\mu\text{mol/L}$), but remains below cytotoxic thresholds. Biofilm is more abundant but less pathogenic on 3D-printed resins. The ECR shows a shorter operating time (5 vs. 19 min) but a higher fracture rate (19% vs. 0%). **Conclusion:** 3D-printed resins are an acceptable alternative for single-tooth temporary restorations, provided post-curing lasts $\geq 15 - 20$ min. The use of 3D-printed resins for bridges or restorations exceeding 6 months is currently

not supported by clinical evidence. Further long-term studies are needed before these indications can be recommended. Clinical trials with follow-up of ≥ 1 year are needed.

Subject Areas

Dentistry

Keywords

3D Printing, Biocompatibility, Cytotoxicity, Monomer Leaching, Temporary Restorations, Fixed Prosthodontics, CAD/CAM, PMMA, Bis-Acrylic Resins, Post-Curing, DLP, SLA

1. Introduction

Temporary prosthetic restorations in fixed dentures are an essential step in prosthetic treatment. During the period between tooth preparation and the placement of the final restoration, they perform essential functions: pulp protection, maintenance of occlusal and periodontal stability, preservation of intermaxillary relationships, and aesthetic anticipation. The quality of the temporary material therefore directly determines subsequent clinical success [1] [2].

For several decades, conventional acrylic resins, particularly self-curing polymethyl methacrylate (PMMA) and bis-acrylic resins, have been the standard for fabricating temporary prostheses [1] [3]. Their widespread use is due to their moderate cost, ease of handling, and generally satisfactory mechanical properties. However, these materials have well-documented biological limitations. Due to incomplete polymerization, they release residual monomers such as methyl methacrylate (MMA), urethane dimethacrylate (UDMA), triethylene glycol dimethacrylate (TEGDMA), and bisphenol A-glycidyl methacrylate (Bis-GMA), whose cytotoxicity toward human gingival fibroblasts and epithelial cells has been established in a dose-dependent manner [4] [5]. Bisacrylic resin, although exhibiting less polymerization shrinkage, is not free of adverse effects [4] [6].

The advent of digital workflows has profoundly changed prosthetic practices. Computer-aided design and manufacturing (CAD/CAM) technologies first introduced resins milled from pre-polymerized blocks [7] [8]. These materials offer a high degree of conversion (DC), reaching approximately 94%, combined with low monomer leaching and excellent biocompatibility [9] [10]. More recently, additive manufacturing via tank photopolymerization, stereolithography (SLA), and digital light processing (DLP) has extended digital fabrication to 3D-printed temporary restorations, offering an attractive cost-to-quality ratio, reduced waste, and short production lead times [7] [11].

However, 3D-printed resins pose a specific biological challenge. The presence of an oxygen-inhibiting layer on the surface can trap unpolymerized monomers

[12] [13]. Several *in vitro* studies have thus reported moderate to severe cytotoxicity, directly influenced by post-processing parameters: post-curing duration and temperature, light intensity, solvent, and post-printing wash duration [13] [14].

To date, no systematic review has synthesized all available data comparing the biocompatibility of 3D-printed resins with that of conventional and CAD/CAM-milled resins for temporary restorations in fixed prosthodontics. Existing studies focus primarily on mechanical properties [1] [15].

Despite the scientific community's growing interest in these innovative materials, several gaps remain in the current literature: the lack of standardized post-processing protocols, methodological heterogeneity in biocompatibility studies, and the absence of long-term *in vivo* clinical data limit the formulation of recommendations based on robust evidence.

Objectives

To synthesize and evaluate the available data on the biocompatibility of 3D-printed resins for temporary restorations in fixed prosthodontics, compared to conventional acrylic resins and CAD/CAM-milled resins.

Secondary objectives:

- Identify the effect of post-processing parameters (post-curing, post-washing) on cytotoxicity.
- Compare the elution profiles of residual monomers according to manufacturing technology.
- Evaluate available *in vivo* clinical data (periodontal response, tissue inflammation).
- Identify methodological gaps and formulate recommendations for future research.

2. Methodology

This systematic review was conducted according to a rigorous protocol to ensure the comprehensiveness and reproducibility of the process, in accordance with the recommendations of the PRISMA 2020 statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol for this systematic review was registered on PROSPERO (CRD420261383298) prior to the start of the literature search.

2.1. Research Question and PICO Framework

Population/Material (P): Polymer resins for fixed temporary prosthetic restorations (crowns and bridges). Included are *in vitro* studies on oral cell lines (gingival fibroblasts, keratinocytes), on organotypic models, as well as *in vivo* studies (animal models or human clinical trials).

Intervention (I): Specimens or restorations fabricated using 3D printing technologies (including digital light processing (DLP), stereolithography (SLA), liquid crystal display (LCD), or vat photopolymerization).

Comparison (C): Conventional resins (self-curing polymethyl methacrylate (PMMA), bis-acrylic resins) and/or polymers machined using subtractive technology (CAD/CAM).

Outcomes (O): The primary evaluation criteria include biological markers of cellular biocompatibility (cell viability rate (%), cytotoxicity) and chemical indicators of polymerization (degree of conversion (DC %), kinetics, and elution profiles of residual monomers in $\mu\text{g/mL}$). Secondary criteria include the inflammatory response (cytokines IL-6, IL-8), oxidative stress (ROS), and bacterial biofilm colonization.

Question: In the available *in vitro* and *in vivo* studies, do 3D-printed temporary resins exhibit a biocompatibility profile that is comparable to, inferior to, or superior to that of conventional resins (acrylic and bis-acrylic) and CAD/CAM-milled resins, and which post-processing parameters influence this profile?

2.2. Information Sources and Search Strategies

A literature search was conducted in the following electronic databases to identify relevant studies: PubMed, Web of Science, OpenAlex, and Scopus.

2.3. Search Equations

Search equations were developed by combining MeSH terms and keywords, using Boolean operators (AND, OR) to maximize the sensitivity and specificity of the results.

2.4. Inclusion and Exclusion Criteria

Inclusion Criteria:

- *In vitro* studies evaluating the cytotoxicity, biocompatibility, or monomer release of resins for fixed, tooth-supported temporary restorations.
- *In vivo* studies (animal or clinical) evaluating the tissue response to 3D-printed temporary resins.
- Studies comparing 3D-printed temporary resins using DLP, SLA, VAT, or PolyJet technologies to conventional or CAD/CAM resins.
- At least one quantitative biological outcome was reported (cell viability, monomer elution, degree of conversion).
- Publication between January 1, 2015, and May 30, 2026.
- Languages: English.
- Publication in a peer-reviewed journal with quantitative data.

Exclusion Criteria:

- Permanent/definitive resins (excluding restorations intended to last ≥ 5 years).
- Resins for removable dentures, implant drilling guides, orthodontics (unless biological evaluation of monomers applies to temporary restorations), and occlusal splints.
- Studies without a comparison group: Absence of conventional or CAD/CAM-milled resin as a control.

- Letters to the editor, editorials, opinion pieces, narrative reviews.
- Studies focusing exclusively on mechanical properties without any biological parameters.

2.5. Definition of Biocompatibility Acceptability Thresholds

To evaluate biocompatibility, the following thresholds were applied in accordance with ISO 10993-5:2009:

- Cell viability: $\geq 70\%$ is considered non-cytotoxic; $< 70\%$ is considered cytotoxic.
- Monomer elution: No standardized threshold exists; values are reported descriptively.
- Inflammatory response (IL-6, IL-8, PGE2): A statistically significant increase ($p < 0.05$) relative to the control is considered a sign of inflammatory reaction.
- Oxidative stress (GSH/GSSG): A significant decrease in GSH or increase in GSSG ($p < 0.05$) is considered a sign of oxidative stress.
- Biofilm: The absence or significantly reduced presence of red-complex bacteria (Socransky classification) is considered a favorable profile.

The overall assessment of biocompatibility took into account all of these parameters, without the assignment of a single quantitative score.

2.6. Study Selection

Study selection was conducted independently by two reviewers, with any disagreements resolved by consensus. All 13 included studies are full peer-reviewed journal articles; no abstract-only records, conference proceedings, or web-only reports were retained.

The study selection process was conducted in two phases and documented using a PRISMA flow diagram:

Phase 1: Screening: Search results from various databases were compiled and exported to the Zotero reference management software to check for duplicates.

Phase 2: Eligibility: Articles selected at the end of the first phase underwent a full-text review. The same two authors independently read each article to confirm that it met all PICO criteria. The reasons for excluding articles not selected for full-text review were recorded.

2.7. Data Extraction

A standardized data extraction form was developed, pre-tested on five pilot studies, and then used by two independent reviewers. Disagreements were resolved by consensus or arbitration by a third reviewer. The extracted variables included: material characteristics (composition, 3D printing technology, post-polymerization, post-washing), biological model, biological tests (viability, monomer elution, cytokines, oxidative stress, biofilm), comparators, compliance with ISO standards, and limitations reported by the authors. **Table 1** presents a summary of the extracted data.

Table 1. Summary of the characteristics and main findings of the included studies (n = 13).

Title & Design	Author (Year) Country	Materials & Technology	PICO Structure	Key Biological Results	Main Conclusions	Reported Limitations
Fabrication of provisional 3D-printed and conventional single crowns on anterior implants: an equivalence RCT	de Souza et al. (2024) Brazil [26]	3D: Cosmos Temp 3D (Yllor)—DLP. Postwash: IPA 2 min. Postcuring: 30 min UV. Comparator: conventional PMMA (Biotone IPN + Duralay)	P: 33 patients (42 crowns). I: 3D crowns. C: Conventional. O: VPI, BoP, FDI (fracture, fit), VAS	Periodontal response (score 1): 90.5% (3D) vs. 95.2% (Conv), p = 0.50. Fractures/retention: 76.2% success (3D) vs. 100% (Conv), p = 0.05. VAS satisfaction: esthetics p = 0.66, phonetics p = 0.32, mastication p = 0.97, comfort p = 1.00.	Comparable clinical performance, except for fracture type (more frequent with 3D).	Reduced exposure surface after cementation vs. laboratory discs.
Organotypic oral mucosa model for the biological evaluation of 3D-printed resins (<i>in vitro</i> , 3D model)	Alamo et al. (2022) [19]	3D: PZ-3D (Prizma) and CS-3D (Cosmos DLP Temp). Postcuring: 1, 10 or 20 min UV. Comparators: AR (Dencor—conventional), CC (VIPI BLOCK—machined CAD/CAM)	P: NOK-Si + hGF coculture in 3D model. I: 3D resins at different post-curing times. C: Conventional and machined. O: Alamar Blue, Live/Dead, UVVis (270 nm)	Viability (1 min postcuring): >70% reduction at all time points. Viability (20 min): cytocompatible, similar to control. Monomer release (270 nm): highest for 1 min post-curing.	Biocompatibility of 3D resins depends on adequate post-processing (≥20 min recommended).	<i>In vitro</i> model does not reproduce the full complexity of the oral cavity <i>in vivo</i> .
Initial biocompatibility of new resins for 3D-printed fixed prostheses (<i>in vitro</i>)	Wuersching et al. (2022) Germany [18]	3D: VSC, ND, VST, TP, P (P Pro Crown & Bridge, Straumann). Comparators: TC, TEL (machined), TEC, PT (conventional)	P: hGF-1. I: 5 3D resins. C: Machined CAD/CAM + conventional. O: Viability (72 h), IL-6, PGE2, GSH/GSSG (oxidative stress)	Viability (72 h): VST = 0.97% (highly toxic); TEC, VSC, ND = toxic; TC (machined) = 78.7% (low toxicity). Oxidative stress: GSSG increased for TEL, VST and P. VSC and P significantly increase PGE2 (inflammatory response). TEC and PT reduce intracellular GSH (antioxidant depletion). All printable resins weakly induce apoptosis.	Most 3D and conventional resins are initially cytotoxic, unlike machined ones.	Initial toxicity assessment only (pure, undiluted eluate); responsible components not identified.
Effect of print orientation on sorption, solubility and monomer elution (<i>in vitro</i>)	Mudhaffer et al. (2025) [23]	3D: ND (C&B MFH), DT (Dima C&B temp), GC (GC temp print), VCP (VarseoSmile CrownPlus), CT (Crowntec)—DLP (ASIGA MAX UV, 385 nm, 50 µm layer). Postcuring: per manufacturer (Otoflash G171, Form Cure, Cara Print LED Cure). Comparators: Lava Ultimate (LU) and Telio CAD (TC) machined CAD/CAM.	P: Specimens (14 × 14 × 1 mm for sorption/solubility; 10 × 10 × 2.2 mm for elution). I: 5 3D-printed resins at 3 orientations (0°, 45°, 90°). C: Machined CAD/CAM resins (LU, TC). O: Sorption/solubility (artificial saliva, 37°C, 90 d, n = 6); monomer elution by UHPLCMS/MS (Bis-EMA, Bis-GMA, TEGDMA, UDMA) in 75% ethanol/water, 1 and 7 d, n = 4; filler content (ash method).	Total elution (µmol/L): GC (87.4) > DT (80.4) > ND (53.2) > VCP (50.8) > CT (47.3) > LU (8.2). Predominant monomers: Bis-EMA for CT/VCP; UDMA for ND/GC; BisGMA for LU. Sorption: ND exceeds ISO 4049 limit (54.5 - 58.4 µg/mm ³ vs. max 40). Negative correlation filler/sorption (r ² = 0.739) and filler/solubility (r ² = 0.896). All eluted concentrations below cytotoxicity thresholds (EC50). Orientation does not affect elution (p = 0.774) but affects sorption (p = 0.008).	Print orientation does not affect monomer elution. Provisional 3D-printed resins (ND, DT, GC) release more monomers than definitive 3D-printed resins (CT, VCP) and than the machined material LU. All materials meet ISO standards except ND (excessive sorption). Eluted monomer concentrations remain below cytotoxic thresholds.	Laboratory concentrations may not reflect those released under clinical conditions (reduced exposure after bonding). The complex oral environment (enzymatic activity, salivary flow, temperature variations, mechanical wear) may amplify release. Possible prolonged lowdose release raises concerns about long-term effects, justifying <i>in vivo</i> studies.
Degree of conversion and elution of residual monomers (<i>in vitro</i>)	Berghaus et al. (2023) Germany [22]	3D: experimental VOCO composite—DLP (SolFlex 350). Comparators: machined CAD/CAM blank + self-curing composite	P: Plate specimens (14 × 14 × 1.9 mm). I: Filled 3D-printed composite (50 wt%) and unfilled 3D resin. C: Machined CAD/CAM + self-curing composite. O: HPLC (TEGDMA, BisGMA, Bis-EMA) in water, ethanol, ethanol/water	DC: 94.3% (CAD/CAM), 95.2% (3D), 89.1% (self-curing). Aqueous elution: below detection limit. Ethanol elution (10 d): self-curing—TEGDMA 1508, Bis-GMA 2089, Bis-EMA 2652; filled 3D—TEGDMA 222, Bis-GMA 389, BisEMA 219. No DC/elution correlation. Eluted monomer concentrations below reported cytotoxic thresholds.	The filled 3D-printed composite (50%) shows a high DC (95.2%) comparable to CAD/CAM, higher than self-curing (89.1%), with low monomer elution. Promising material for provisional crowns and bridges.	Industrial process not reproduced; no total monomer extraction; salivary flow not accounted for; additional cell tests needed; FTIR light source different from the DLP printer.

Continued

Biochemical interaction between provisional prosthetic materials and saliva (<i>in vitro</i>)	Pantea <i>et al.</i> (2021) [27] Romania	3D: NextDent C&B MFH. Comparators: Superpont C + B (self-curing), Telio CAD (machined), SR Chromasit (lab composite)	P: Human saliva (20 volunteers). I: 3D NextDent resin. C: Self-curing, machined, lab composite. O: IL-6, TNF- α , oxidative stress (uric acid, GGT) after 12 h	IL-6/albumin: 3D = 19.3; machined = 95.4; self-curing = 91.3 pg/mg. TNF α /albumin: 3D = 0.25; machined = 0.37; self-curing = 0.61.	The 3D resin induces the lowest production of inflammatory cytokines among the tested materials.	Small number of materials (n = 4), small saliva sample (n = 20), short incubation (12 h), COVID context.
Biocompatibility and biofilm formation on provisional implant restorations (<i>in vitro</i>)	Parakaw <i>et al.</i> (2023) [17]	3D: NextDent C&B MFH (ND). Machined: VIPIblock (VP). Conventional: Unifast Trad (UT), Protemp 4 (PT)	P: hGF-1. I: ND vs. VP vs. UT, PT. C: Machined + conventional. O: MTT (72 h), Calcein-AM, SEM, <i>P. gingivalis</i> biofilm (PCR)	MTT viability: >90% for all (non-cytotoxic). Biofilm thickness: UT = 23.1 μ m; ND = 13.2 μ m; VP = 7.5 μ m. <i>P. gingivalis</i> PCR: detected everywhere (1000 - 4000 CFU), no significant difference (p = 0.39).	All resins are cytocompatible, but machined PMMA (VP) is the most favorable against biofilm.	<i>In vitro</i> study (does not reproduce oral complexity), n = 3 per group (small sample), no artificial aging, complementary <i>in vivo</i> studies needed.
Cytotoxicity of 3D resins on periodontal ligament cells (PDLhTERT) (<i>in vitro</i>)	Folwaczny <i>et al.</i> (2023) [28]	3D: NextDent MFH, 3Delta temp, GC temp, Freeprint temp. Comparators: Luxatemp (conventional), Grandio disc (CAD/CAM)	P: PDL-hTERT. I: 4 3D resins. C: Luxatemp + Grandio disc. O: XTT (viability), IL-6/IL-8 (ELISA). ISO 10993-5	Viability (direct contact): Luxatemp and 3Delta temp < 10% (p < 0.001). NextDent MFH, GC temp, Freeprint temp, Grandio disc: viability > 70% (non-cytotoxic). 3Delta temp = exception among the 3D resins.	Luxatemp and 3Delta temp severely affect PDL cells. The other 3D and CAD/CAM resins are safe.	Temporary restorations generally have no direct contact with PDL cells (eluates may indirectly affect the periodontal situation by altering bacterial virulence factors).
Biomechanical properties of a 3D-printed polymer for provisional restorations (<i>in vitro</i>)	Britto <i>et al.</i> (2022) [16]	3D: Cosmos Temp (Yllor). Comparators: Yprov Bisacryl (BA), thermal acrylic (AR)	P: Primary human gingival fibroblasts. I: Cosmos Temp 3D. C: BA + AR. O: MTT, SRB (72 h)	SRB viability (72 h): 3D = 92.9%; BA = 90.8%; AR = 71.9%. Conventional acrylic is the least viable.	The 3D polymer shows adequate behavior and better viability than conventional acrylic.	Degree of conversion and density not assessed; lack of studies on the aging of 3D-printed materials.
Effects of printing and post-curing protocols on 3D resins (<i>in vitro</i>)	Pacheco <i>et al.</i> (2025) [20]	3D: PZP (Prizma Bio Prov), SPP (Smart Print Bio Temp). Tm vs. Tc; post-curing 5, 10, 15 min. Comparator: Dencor acrylic resin	P: NOK-Si keratinocytes. I: 2 3D resins at different protocols. C: Conventional acrylic. O: MTT (24/72 h), monomer leaching (270 nm). ISO 10993-5	Cytocompatibility: all 3D resins > 80% viability. Monomer leaching: inversely proportional to post-curing time.	The resins are cytocompatible, but post-curing significantly affects monomer release.	A single printer and a single UV chamber; whiteness index not calculated; color stability over time not assessed; biological tests on extracts only (no direct contact); <i>in vitro</i> study (validation under oral conditions needed).
Next-generation dental materials—biofilm formation (<i>in vitro</i>)	Uehara <i>et al.</i> (2025) [25]	3D: Cosmos Temp (G1), Prizma 3D Bio Crown (G2), Prizma 3D Bio Prov (G3). Comparator: Classico acrylic resin (G4)	P: Multi-species biofilm (39 species). I: 3 3D resins. C: Conventional acrylic. O: Metabolic activity, DNA-DNA hybridization	Biofilm metabolic activity: Cosmos (G1) = 131.9% vs. Classico = 100% (more active biofilm but no longer pathogenic—absence of the red complex). <i>P. gingivalis</i> : less present on G2 and G3 (3D) than on G4 (acrylic).	Biofilm on 3D resins is less pathogenic (absence of red complex bacteria) than on conventional acrylic resin.	No polishing assessment; absence of salivary pellicle (key modulator of bacterial adhesion <i>in vivo</i>); <i>in vitro</i> incubation time may influence results; <i>in vivo</i> adhesion profiles may differ from those observed <i>in vitro</i> .
Influence of surface properties on multispecies biofilm (<i>in vitro</i>)	Wuersching <i>et al.</i> (2026) [24]	3D: VSC, ND, VST, TP. P. Comparators: machined PMMA (TC, TEL), conventional (TEC, PT), zirconia (ZR)	P: Mature oral biofilm (72 h). I: 5 3D resins. C: Machined, conventional, zirconia. O: Biofilm mass (gentian violet), CFU, interfacial tension	Biofilm mass: no significant difference between 3D, machined and conventional. CFU: similar bacterial accumulation between 3D and reference materials.	3D resins do not differ significantly from conventional or machined materials for multispecies biofilm formation.	Absence of salivary pellicle (key modulator of bacterial adhesion <i>in vivo</i>); no artificial aging or functional loading; limited number of materials (small sample); observed correlations need validation with larger datasets; roughness measured only by Ra (does not capture full topographic complexity).

Continued

Effect of enzymatic degradation and hydrolysis on 3D provisional resins (<i>in vitro</i>)	Berghaus et al. (2022) [21]	3D: experimental VOCO composite—DLP. Comparators: machined CAD/CAM + self-curing	P: Cholesterol esterase (enzymes) + PBS (hydrolysis). I: Experimental 3D composite. C: Machined + self-curing. O: HPLC-DAD (BisGMA, TEGDMA) over 22 d	Enzymatic degradation: no effect on 3D or CAD/CAM; increased elution for self-curing. Eluted Bis-GMA (4 d): 3D = 1.6 µg/mm ² ; CAD/CAM = 1.4 µg/mm ² .	The 3D composite behaves like the machined material under chemical, enzymatic and hydrolytic degradation.	n = 3 only (limited statistical power).
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Abbreviations: 3D, three-dimensional printing; AR, conventional/thermal acrylic resin; BA, bis-acrylic resin; BoP, bleeding on probing; CAD/CAM, computer-aided design/manufacturing; CFU, colony-forming units; DC, degree of conversion; DLP, digital light processing; ELISA, enzyme-linked immunosorbent assay; FDI, World Dental Federation criteria; GGT, gamma-glutamyl transferase; GSH/GSSG, reduced/oxidized glutathione; hGF, human gingival fibroblasts; HPLC, high-performance liquid chromatography; IPA, isopropyl alcohol; ISO, International Organization for Standardization; PDL-hTERT, hTERT-immortalized periodontal ligament cells; PMMA, polymethyl methacrylate; RCT, randomized clinical trial; SEM, scanning electron microscopy; SLA, stereolithography; SRB, sulforhodamine B; TEGDMA, triethylene glycol dimethacrylate; UDMA, urethane dimethacrylate; UHPLC-MS/MS, ultra-high-performance liquid chromatography-tandem mass spectrometry; VAS, visual analog scale; VPI, visible plaque index; XTT, tetrazolium salt viability assay; ZR, zirconia.

2.8. Assessment of Risk of Bias

The risk of bias was assessed by two independent reviewers. For the 12 *in vitro* studies, the QUIN tool (12 criteria, score out of 24, thresholds: low ≥ 17 , moderate 12 - 16, high < 12) was used. For the randomized clinical trial, the Cochrane RoB 2.0 tool was used. Disagreements were resolved by consensus or arbitration by a third reviewer.

2.9. Data Synthesis and Analysis

Narrative synthesis: Organized by biological outcome (cytotoxicity, elution, degree of conversion), printing technology, and post-processing parameters.

Meta-analysis: Not performed due to significant clinical and methodological heterogeneity among the studies (variability in resins, post-polymerization protocols, cell models, and viability assays). A narrative synthesis was preferred (PRISMA 2020).

3. Results

3.1. Study Selection and General Characteristics

A total of 822 studies were identified through the literature search. After removing duplicates (n = 208) and studies deemed outside the scope of the review (n = 533) based on their titles and abstracts, 81 studies were reviewed in full text. In total, 13 studies were eligible for inclusion in the review (**Figure 1**).

Study Characteristics

The main characteristics of the included studies are summarized in **Table 1**. Of the 13 included studies, 12 were *in vitro* studies and one was a randomized clinical trial. The publications span the years 2021 to 2026.

The most frequently evaluated 3D-printed resin was NextDent C&B MFH (n = 5), followed by Cosmos Temp (n = 3). Comparators included self-curing acrylic resins (n = 8), machined CAD/CAM blocks (n = 7), and bis-acrylic composites (n = 4).

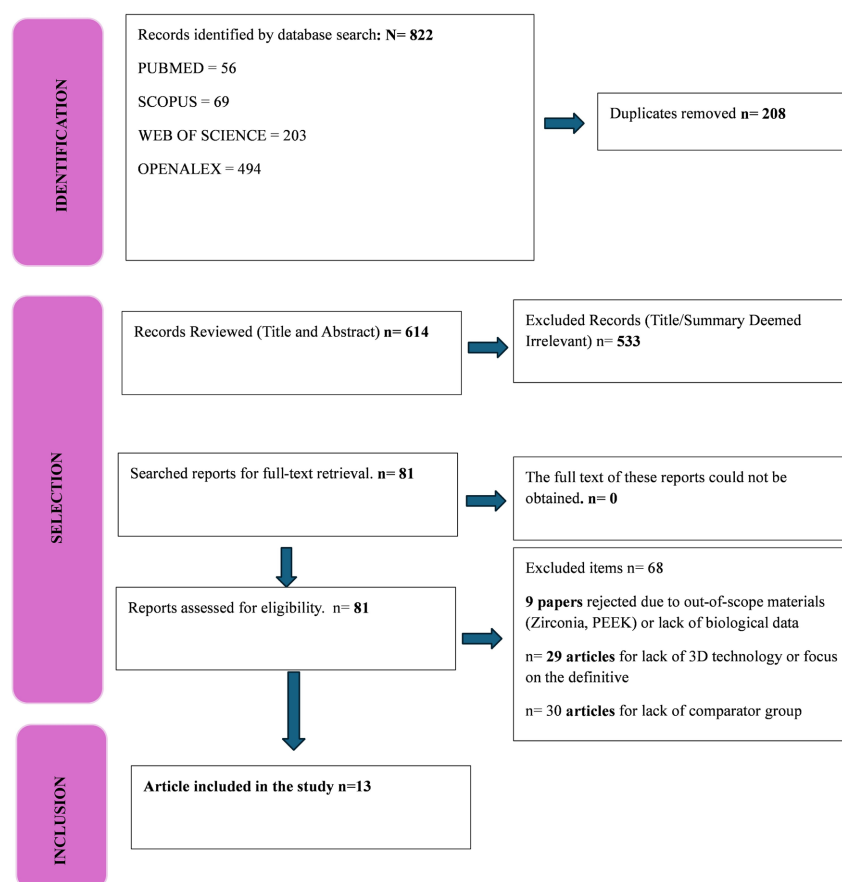


Figure 1. PRISMA flowchart 2020.

Biocompatibility was evaluated in 10 studies (cell viability, inflammatory response, oxidative stress). Monomer elution was quantified in 6 studies. Surface properties and biofilm formation were examined in 5 studies. The sole clinical trial evaluated FDI criteria, periodontal indices, and patient satisfaction.

3.2. Narrative Synthesis of the Data

The synthesis of results is organized according to three principal modifiers identified as sources of heterogeneity between studies: 1) extraction conditions, 2) cell model, and 3) post-polymerization protocol.

3.2.1. Effect of Extraction Conditions

Studies using pure undiluted extracts (Wuersching *et al.*, 2022) reported more severe cytotoxicity than those using diluted extracts or limited direct contact (Alamo *et al.*, 2022; Folwaczny *et al.*, 2023). Berghaus *et al.* (2023) showed that elution into water (simulating saliva) was undetectable, whereas it was quantifiable in ethanol (worst-case scenario). These methodological differences partly explain the disparities observed across studies.

3.2.2. Effect of the Cell Model

Primary gingival fibroblasts (Britto *et al.*, 2022; Wuersching *et al.*, 2022) showed

variable sensitivity depending on the materials, while oral keratinocytes (NOK-Si) (Alamo *et al.*, 2022; Pacheco *et al.*, 2025) showed generally lower sensitivity. Periodontal ligament cells (PDL-hTERT) (Folwaczny *et al.*, 2023) were particularly sensitive to direct contact with conventional resins.

3.2.3. Effect of the Post-Polymerization Protocol

Extending post-polymerization time improves the cytocompatibility of 3D-printed resins. Alamo *et al.* (2022) observed a reduction of >70% in cell viability with 1 min of post-polymerization, whereas 20 min yielded a level comparable to CAD/CAM-milled resins. Pacheco *et al.* (2025) confirmed that monomer leaching is inversely proportional to post-polymerization time.

3.2.4. Synthesis of Results by Outcome Cytotoxicity and Monomer Elution

The results show that biocompatibility depends on the type of printed resin: Britto *et al.* (2022) demonstrated that the Cosmos Temp printed resin exhibited a viability rate of 92.9%, which was higher than that of acrylic resin (71.9%) [16]; similarly, Parakaw *et al.* (2023) reported that NextDent C&B MFH was non-toxic to gingival fibroblasts [17]. Conversely, Wuerschling *et al.* (2022) observed that several printable resins (VSC, ND, VST, TP, P) were severely toxic, with viability close to 0% for VarseoSmile Temp [18].

Alamo *et al.* (2022) [19] and Pacheco *et al.* (2025) [20] demonstrated that cytotoxicity and monomer leaching depended on post-polymerization time: 1 minute induced a >70% reduction in cellular metabolism and high leaching, whereas 15 - 20 minutes yielded a profile similar to that of CAD/CAM resins.

Berghaus *et al.* (2022, 2023) [21] [22] detected BisGMA in the printed eluates, with maximum elution in ethanol and none in water. Mudhaffer *et al.* (2025) demonstrated that printed temporary resins exhibited higher elution (53 - 87 µmol/L) than printed final resins (50 - 51 µmol/L) and the milled Lava Ultimate block (7.6 µmol/L), with no effect of print orientation [23].

Surface Properties and Biofilm Formation

Surface roughness and texture (influenced by the material and manufacturing technique) played an important role, with smoother surfaces (machined PMMA) exhibiting less biofilm.

Parakaw *et al.* (2023) [17] and Wuerschling *et al.* (2026) [24] reported that all tested restorations were non-toxic and promoted good fibroblast adhesion, but differed in the amount of biofilm formed.

Wuerschling *et al.* (2026) identified a moderate positive correlation between surface roughness and the number of viable bacteria [24].

Uehara *et al.* (2025) observed that 3D-printed resins exhibited greater biofilm formation than acrylic resin, but their microbiological profile was less pathogenic (absence of the red complex) [25].

3D-printed resins for temporary restorations demonstrate generally acceptable performance in terms of biocompatibility and leaching, provided an adequate post-polymerization protocol is followed (≥15 - 20 minutes). Certainty of evidence was

not formally graded using GRADE in this review. However, the overall certainty is considered low to very low for all outcomes: cytotoxicity and monomer elution data derive from heterogeneous *in vitro* studies with moderate risk of bias; biofilm data are limited to three studies with variable protocols; and clinical evidence is based on a single RCT with short follow-up. These limitations should be considered when interpreting the conclusions.

3.3. Results of the Risk of Bias Assessment

Among the 12 *in vitro* studies, only one (Uehara *et al.*, 2025) had a low risk of bias (score 17/24). The other 11 studies (92%) had a moderate risk of bias (scores 12 - 15/24). The most frequently unreported criteria were assessor blinding (missing in 11 studies), randomization (missing in 11 studies), and sample size calculation (missing or incomplete in 10 studies). The clinical trial by de Souza *et al.* [26] (2024) showed a low risk of bias across all five domains of the Cochrane RoB 2.0 tool. No studies were excluded based on quality.

4. Discussion

This systematic review synthesized the available data on the biocompatibility of 3D-printed resins for temporary restorations in fixed prosthodontics, compared to conventional resins (acrylic, bis-acrylic) and CAD/CAM-milled resins. Our results show significant heterogeneity in biocompatibility profiles, largely dependent on the parameters of chemical composition, post-treatment, and the biological model used. The overall certainty of the evidence remains limited due to the predominance of *in vitro* studies, methodological heterogeneity of protocols, and the small number of available clinical studies.

Cytotoxicity: Cell viability results vary considerably depending on the printed resin tested. Britto *et al.* (2022) reported a viability of 92.9% for Cosmos Temp, higher than that of conventional acrylic resin (71.9%) [16].

Parakaw *et al.* (2023) observed viability > 90% for NextDent C&B MFH, concluding that it was non-cytotoxic [17]. Folwaczny *et al.* (2023) demonstrated that NextDent MFH, GC Temp, and Freeprint Temp exhibited viability > 70% in periodontal ligament cells, the threshold for non-cytotoxicity according to ISO 10993-5 [28].

In contrast, Wuerschling *et al.* (2022) reported viability close to 0% for VarseoS-mile Temp and severe cytotoxicity for several printable resins (VSC, ND, VST, TP, P) [18]. Several methodological factors may account for these discrepancies. First, Wuerschling *et al.* [18] used undiluted pure extracts (in accordance with ISO 10993-12), whereas other studies used diluted extracts or direct contact with cells, which artificially lowers the apparent cytotoxicity. Second, cell type influences sensitivity: Wuerschling *et al.* [18] used primary human gingival fibroblasts, which are more sensitive than the immortalized cell lines used by Britto *et al.* [16] (2022).

Intra-category variability of printed resins. Folwaczny *et al.* (2023) demon-

strated that 3Delta Temp was severely cytotoxic (viability < 10%), whereas NextDent MFH, GC Temp, and Freeprint Temp were non-cytotoxic (> 70%) [28]. Similarly, Wuerschling *et al.* (2022) reported considerable differences between VarseoSmile Temp (viability close to 0%), NextDent (toxic), and the other resins [18].

This variability can be attributed to several factors: 1) chemical composition (monomers, photoinitiators, stabilizers); 2) filler content (filled resins release fewer monomers because the organic fraction is reduced); 3) adherence to the post-polymerization protocols recommended by the manufacturer. It is therefore impossible to draw a general conclusion about “3D-printed resins”: the answer is product-specific and depends strictly on manufacturing conditions.

The variability in post-processing protocols across studies largely explains the contradictory results observed in the literature [20]. Alamo *et al.* (2022) [19] and Pacheco *et al.* (2025) [20] demonstrated that a 1-minute post-polymerization reduced cellular metabolism by >70%, whereas a duration of 15 to 20 minutes achieved a biocompatibility profile similar to that of milled resins.

4.1. Role of Post-Polymerization

Alamo *et al.* (2022) [19] and Pacheco *et al.* (2025) [20] demonstrated a clear inverse relationship between post-polymerization duration and monomer release. A 1-minute post-curing time was insufficient and resulted in severe cytotoxicity, whereas a duration of 15 to 20 minutes achieved a biocompatibility profile equivalent to that of milled resins.

However, the heterogeneity of protocols across studies is striking. Post-polymerization durations vary from 5 to 30 minutes depending on the manufacturer, and washing conditions (solvent, duration, method) are rarely standardized. Several studies do not report light intensity (mW/cm²) or the exact wavelength, which limits reproducibility and comparability between studies. As Alamo *et al.* (2022) [19], post-polymerization affects not only monomer release but also surface properties. Prolonged post-polymerization can increase roughness or alter surface chemistry, thereby influencing bacterial adhesion.

Monomer elution: A key material-dependent mechanism. Mudhaffer *et al.* (2025) quantified the total elution of six 3D-printed resins [23]. The printed temporary resins (NextDent C&B MFH, Dima C&B temp, GC temp print) released more monomers (53 - 87 µmol/L) than the printed permanent resins (VarseoSmile Crown-plus, Crowntec: 47 - 51 µmol/L) and than the milled Lava Ultimate block (7.6 µmol/L). This difference can be explained by the chemical composition: temporary resins contain monomers with lower molecular weights (UDMA, TEGDMA) that are more mobile and more easily leachable, whereas permanent resins incorporate more mineral fillers, reducing the extractable organic fraction.

Berghaus *et al.* (2023) demonstrated that the 50% filled 3D-printed composite exhibited a degree of conversion of 95.2%, comparable to milled blocks (94.3%) and higher than self-curing resins (89.1%) [22]. Importantly, no correlation was found between the degree of conversion and monomer elution, suggesting that

other factors, such as polymer chain mobility, microporosity, and hydrophilicity, are key determinants in the release of residual monomers.

Berghaus *et al.* (2022) supplemented these findings by demonstrating that the 3D-printed composite behaved similarly to the machined material in response to enzymatic and hydrolytic degradation, whereas the self-curing material exhibited greater elution of Bis-GMA and TEGDMA [21]. All concentrations of eluted monomers remain below the EC50 values reported in the literature. However, as Mudhaffer *et al.* (2025) point out, *in vitro* conditions (extraction in a fixed volume, without renewal) do not replicate continuous salivary flow or chronic low-dose exposure, the genotoxic or sensitizing effects of which have not been evaluated [23].

Biofilm: Quantity vs. pathogenicity. The surface properties of 3D-printed resins differ from those of machined and conventional resins, with implications for biofilm formation. Parakaw *et al.* (2023) demonstrated that milled PMMA (VIPI block) exhibited the thinnest biofilm (7.5 µm), compared to 13.2 µm for NextDent C&B MFH and 23.1 µm for the self-curing Unifast Trad [17]. This result is consistent with the lower surface roughness of milled blocks, achieved through an industrial process involving high pressure and temperature.

Uehara *et al.* (2025) provided a more nuanced perspective: while 3D-printed resins (Cosmos Temp, Prizma 3D Bio Crown, Prizma 3D Bio Prov) did form a more abundant biofilm than conventional acrylic resin, this biofilm was less pathogenic, with an absence of bacteria from the red complex (*P. gingivalis*, *T. forsythia*, *T. denticola*). This result suggests that the surface chemistry of 3D-printed resins selects for a less virulent microbiota, potentially less harmful to periodontal tissues [25].

Wuersching *et al.* (2026) partially confirmed this result, showing that there was no significant difference in biofilm mass or CFU between 3D-printed, milled, and conventional resins. They identified a strong negative correlation between total interfacial tension and biofilm mass, and a moderate positive correlation between roughness (Ra) and the number of viable bacteria. Surface physicochemical properties (free energy, hydrophobicity, roughness) are therefore major determinants of bacterial colonization [24].

Clinical data: Only one randomized clinical trial was included (de Souza *et al.*, 2024). This trial compared 42 temporary crowns (21 3D-printed, 21 conventional) on anterior implants. The results showed a shorter operative time for 3D printing (5 vs. 19 minutes, $p < 0.001$), but a higher rate of catastrophic fractures (19% vs. 0%, $p = 0.05$) and lower clinical success (76.2% vs. 100%). Patient satisfaction (aesthetics, phonetics, mastication, comfort) and periodontal indices (VPI, BoP) were similar between the two groups. These results indicate that, from a biological and aesthetic standpoint, 3D-printed crowns are equivalent to conventional crowns, but their mechanical durability is inferior. No other clinical studies were identified, which constitutes a major gap in the literature [26].

This review has several limitations: The majority of studies are *in vitro* and do

not replicate oral complexity (salivary flow, acquired pellicle, mature biofilm); heterogeneity of post-polymerization protocols prevents any robust meta-analysis; lack of long-term clinical data (>1 year); risk of publication bias (underrepresentation of negative results). Finally, *in vitro* studies use pure extracts or direct contact conditions that do not reflect *in vivo* saliva dilution and turnover.

4.2. Implications for Research and Practice

For research: Future studies must accurately report post-polymerization parameters (duration, temperature, mW/cm², wavelength, washing solvent), comply with ISO 10993-5 and -12 standards, and include machined and conventional controls. Randomized clinical trials with a follow-up period of ≥1 year are urgently needed to evaluate not only biocompatibility but also mechanical durability.

For clinical practice: The biocompatibility of printed resins depends strictly on adherence to the manufacturer's protocols, with post-curing of ≥15 - 20 minutes (Alamo *et al.*, 2022 [19]; Pacheco *et al.*, 2025) [20] and adequate rinsing. The use of 3D-printed resins for long-term restorations (>6 months) or for multi-unit bridges is currently not supported by clinical evidence: the sole included trial (de Souza *et al.*, 2024) [26] reported a fracture rate of 19% vs. 0% for conventional resins, and no other clinical studies are available. Further randomized trials with longer follow-up are needed before these indications can be recommended. For single-unit restorations, they may be an acceptable alternative to conventional resins, provided the patient is informed and closely monitored. The choice of a 3D-printed resin should be guided by validated biocompatibility data for that specific product, not by a generic trust in the technology.

5. Conclusions

This systematic review compared the biocompatibility of 3D-printed resins for fixed temporary restorations with that of conventional and CAD/CAM-milled resins, based on 13 studies (12 *in vitro*, 1 randomized clinical trial). 3D-printed resins do not exhibit a uniform biocompatibility profile: their cytotoxicity is product-specific and critically depends on post-processing parameters. A 1-minute post-curing period induces severe cytotoxicity, whereas a duration of 15 to 20 minutes allows for a level comparable to that of milled resins. Monomer elution is higher for printed temporary resins but remains below cytotoxic thresholds.

In clinical practice, printed resins can be used for single-tooth restorations provided that post-curing lasts ≥ 15 - 20 minutes.

Future research: Clinical trials with a follow-up period of ≥1 year are urgently needed. Studies must report duration, temperature, light intensity, wavelength, and rinsing solvent, in compliance with ISO 10993-5 and -12 standards.

Conflicts of Interest

The authors declare no conflicts of interest.

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