Biomaterials Advances 190 (2027) 215136

Contents lists available at ScienceDirect

Biomaterials Advances

journal homepage: www.journals.elsevier.com/materials-science-and-engineering-c

Dental biomaterials-on-chip: A scoping review of dynamic material–tissue–biofilm models☆

Rene Garcia-Contreras [a,*], Febe Carolina Vazquez-Vazquez [b]

[a] Nanostructures and Biomaterials Area, Interdisciplinary Research Laboratory (LII), National School of Higher Studies (ENES), Leon Unit, National Autonomous University of Mexico (UNAM), Leon, Mexico
[b] Biomaterials Laboratory, Graduate Studies and Research Division, National Autonomous University of Mexico (UNAM), Mexico

ARTICLE INFO

Keywords:
Organ-on-a-chip
Dental biomaterials
Microfluidics
Oral biofilm
Biocompatibility
Translational dentistry

ABSTRACT

The preclinical evaluation of dental biomaterials remains largely dependent on static *in vitro* assays that provide limited insight into dynamic material–tissue–biofilm interactions. Microfluidic lab-on-a-chip (LoC) and organ-on-a-chip (OoC) platforms can reproduce selected features of the oral microenvironment, including controlled transport, tissue barriers, three-dimensional cellular organization, microbial challenge, and time-resolved monitoring. This scoping review with structured narrative synthesis mapped peer-reviewed dental and oral microfluidic studies published through July 27, 2026. An initial search of PubMed/MEDLINE, Scopus, Web of Science Core Collection, ScienceDirect, Embase, and IEEE Xplore was supplemented by an updated focused search, Google Scholar, and backward and forward citation tracking. Of 114 records identified, 82 remained after duplicate removal, 46 full-text reports were assessed, and 28 sources were included: 21 original experimental studies and seven dental/oral reviews. Original platforms comprised tooth and dentin–pulp models, oral mucosa and gingival barriers, periodontal and bone–vascular interfaces, dental pulp angiogenesis systems, peri-implant models, and dynamic host–microbe platforms. These systems enabled trans-barrier exposure, controlled flow and shear, long-term barrier monitoring, biomaterial cytotoxicity testing, inflammatory modeling, biofilm challenge, and regenerative assessment. Nevertheless, fluidic parameters, adsorption, oxygenation, comparator assays, and interlaboratory reproducibility were inconsistently reported. None of the included original dental studies used artificial intelligence for externally validated predictive inference. A conceptual Modular Dental Microfluidic Ecosystem Platform is presented as an evidence-informed future framework. Current dental chips should therefore be regarded as complementary mechanistic and qualification tools rather than replacements for standardized testing.

1. Introduction

Dental biomaterials are essential for restorative, endodontic, periodontal, implant, and regenerative dentistry. However, their biological performance is still commonly evaluated using conventional static *in vitro* assays such as monolayer cell cultures, extract-based cytotoxicity tests, agar diffusion assays, and endpoint viability measurements. Although these approaches remain useful for preliminary screening and regulatory standardization, their results offer limited information about the dynamic biological events that occur in the oral environment.

The oral cavity represents a dynamic and physiologically complex microenvironment in which dental biomaterials are continuously exposed to salivary flow, dentinal fluid movement, gingival crevicular fluid within periodontal pockets, microbial biofilm formation, pH variations, enzymatic activity, mechanical loading, immune-mediated responses, and interactions among multiple oral tissue compartments. These biological and physicochemical conditions are difficult to reproduce using traditional static culture models. Recent reviews emphasize that current *in vitro* models often fail to emulate the interaction among oral microbiota, host immune response, biomaterials, and fluctuating physicochemical signals, limiting their translational predictability [1].

Lab-on-a-chip (LoC) and organ-on-a-chip (OoC) technologies have emerged as advanced microphysiological systems capable of reproducing tissue-level functions under controlled microfluidic conditions.

☆ This article is part of a Special issue entitled: 'Lab-on-a-Chip' published in Biomaterials Advances.

* Corresponding author.
E-mail address: rgarciac@enes.unam.mx (R. Garcia-Contreras).

https://doi.org/10.1016/j.bioadv.2026.215136
Received 13 June 2026; Received in revised form 14 August 2026; Accepted 24 August 2026
Available online 28 August 2026
2772-9508/© 2026 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

These platforms allow the incorporation of fluid flow, chemical gradients, shear stress, cellular co-cultures, 3D cultures, biological barriers, biomaterial interfaces, and real-time imaging. In dentistry, OoC models have been proposed for studying tooth–biomaterial interactions, dental pulp physiology, periodontal inflammation, oral mucosa, salivary glands, oral cancer, implant-associated infections, and biofilm dynamics [2–4].

Therefore, the incorporation of LoC systems into dental biomaterials research represents a methodological transition from static, reductionist assays toward dynamic, potentially more physiologically representative, and biologically integrated platforms. This scoping review with structured narrative synthesis maps current dental and oral microfluidic technologies and introduces a conceptual Modular Dental Microfluidic Ecosystem Platform integrating biomaterial release, concentration gradients, host-cell responses, microbial challenges, biosensing, and artificial intelligence-assisted exploratory analysis. The proposed platform is an evidence-informed theoretical framework and has not been fabricated or experimentally validated.

2. Methods

2.1. Review design

This study was conducted as a scoping review with structured narrative synthesis to identify, map, and critically discuss current applications of LoC, OoC, and related microfluidic platforms in dentistry and dental biomaterials research. A scoping approach was selected because the evidence encompasses heterogeneous engineering, biological, methodological, and translational studies that are not suitable for quantitative pooling.

Reporting was guided by the PRISMA extension for Scoping Reviews and PRISMA-S. PRISMA 2020 principles were additionally used to improve transparency in record identification, screening, eligibility assessment, and reporting [5–7]. Scale for the Assessment of Narrative Review Articles (SANRA) was consulted only as a general writing and transparency reference for the narrative synthesis and was not applied as a risk-of-bias instrument for the included studies [8].

The review protocol was not prospectively registered because scoping reviews are not eligible for registration in PROSPERO. Although alternative repositories are available, the search and screening process had already begun when registration was considered; therefore, retrospective registration was not undertaken, as it would not represent genuine prospective documentation. To ensure methodological transparency and reproducibility, the eligibility criteria, database-specific search strategies, study-selection procedures, and data-charting variables are reported in detail in the manuscript and supplementary material.

2.2. Research question

The review was guided by the following research question: How can microfluidic lab-on-a-chip and organ-on-a-chip platforms be integrated into dental biomaterials research to support dynamic, human-relevant, and potentially more informative evaluation of material–tissue–biofilm interactions?

To structure the search, the research question was organized using a modified PEO framework: *Population/biological context*: dental, oral, pulpal, dentin–pulp, periodontal, gingival, salivary, peri-implant, and oral biofilm microenvironments relevant to biomaterial–tissue–biofilm interactions; *Exposure/technology*: LoC, OoC, microfluidic systems, microphysiological platforms, tooth-on-chip, dentin-on-chip, pulp-on-chip, periodontal-on-chip, gingiva-on-chip, implant-on-chip, and biofilm-on-chip systems; *Outcome/application*: dynamic dental biomaterial evaluation, material release kinetics, cytotoxicity, antimicrobial performance, biofilm maturation, inflammatory response, tissue regeneration, barrier function, host–material–pathogen interactions, biosensing, predictive modeling, and artificial intelligence (AI)-assisted analysis. Because the literature included original experimental studies, reviews, methodological papers, AI perspectives, and regulatory publications, the sources were classified according to study type before data extraction and synthesis.

2.3. Information sources and search period

A comprehensive initial literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science Core Collection, ScienceDirect, Embase, and IEEE Xplore. Google Scholar was used only as a supplementary source for citation tracking and to identify additional relevant publications not retrieved through the primary database search. The inclusion of engineering-oriented databases, particularly IEEE Xplore, was considered essential because LoC, OoC, and microfluidic technologies are frequently reported in bioengineering, biomedical device, microfabrication, and analytical platform journals before being translated into dental, oral biology, or biomaterials research. In addition, the reference lists of selected articles and recent reviews were manually screened to identify further studies that may not have been captured by the electronic search strategy.

The initial search included articles published from January 2015 to June 2026. Following peer-review comments, a focused update search was conducted through July 27, 2026 using PubMed/MEDLINE, Google Scholar, backward and forward citation tracking, named dental chip models, and reviewer-recommended references. Seminal pre-2015 publications could be retained as background but were not counted in the primary evidence set unless they met the predefined eligibility criteria.

Grey-literature sources, including ClinicalTrials.gov, bioRxiv, medRxiv, and the Open Science Framework, were checked for potentially overlooked dental or oral platforms. Non-peer-reviewed records were not included in the evidence synthesis but were documented during eligibility assessment.

2.4. Search terms and Boolean strategy

The search strategy combined controlled vocabulary terms, including MeSH terms when available, with free-text keywords related to microfluidic technologies, dental and oral microenvironments, biomaterials, biological responses, biofilm behavior, biosensing, and artificial intelligence. The strategy was structured into four conceptual blocks to capture the convergence between dental biomaterials and lab-on-a-chip/organ-on-a-chip technologies.

The first block focused on microfluidic and microphysiological technologies and included the following terms: *"organ-on-a-chip", "organ chip", "organs-on-chips", "lab-on-a-chip", "microfluidic*", "microphysiological system*", "biofilm-on-chip", "tooth-on-a-chip", "dentin-on-a-chip", "pulp-on-a-chip", "gingiva-on-a-chip", "periodontal-on-a-chip", and "implant-on-a-chip"*.

The second block addressed the dental, oral, and craniofacial biological context and included: *dentistry, dental, tooth, dentin, pulp, "dental pulp", odontoblast*, endodontic*, periodontal, periodontitis, gingiva, "oral mucosa", saliva, salivary, peri-implantitis, implant, craniofacial, and "oral biofilm"*.

The third block focused on biomaterials and biological applications, including: *biomaterial*, scaffold*, hydrogel*, adhesive*, resin, "calcium silicate", bioceramic*, titanium, zirconia, "bioactive material*", "antimicrobial material*", cytotoxicity, biocompatibility, "material release", "release kinetics", degradation, inflammation, regeneration, angiogenesis, mineralization, "drug testing", "material testing", "host–material interaction", "host–pathogen interaction", and "material–tissue interface"*.

The fourth block included predictive and analytical technologies relevant to advanced biomaterial evaluation: "artificial intelligence", "machine learning", "deep learning", "image analysis", "predictive model", biosensor*, "real-time monitoring", "automated analysis", and*

"computational modeling".

The general search string was adapted for each database and combined the technology, dental/oral context, and biomaterials/application blocks as follows:

("organ-on-a-chip" OR "organ chip" OR "organs-on-chips" OR "lab-on-a-chip" OR microfluidic OR "microphysiological system*" OR "biofilm-on-chip" OR "tooth-on-a-chip" OR "dentin-on-a-chip" OR "pulp-on-a-chip" OR "gingiva-on-a-chip" OR "periodontal-on-a-chip" OR "implant-on-a-chip") AND (dentistry OR dental OR tooth OR dentin OR pulp OR "dental pulp" OR odontoblast* OR endodontic* OR periodontal OR periodontitis OR gingiva OR "oral mucosa" OR saliva OR salivary OR peri-implantitis OR implant OR craniofacial OR "oral biofilm") AND (biomaterial* OR scaffold* OR hydrogel* OR adhesive* OR resin OR "calcium silicate" OR bioceramic* OR titanium OR zirconia OR "bioactive material*" OR "antimicrobial material*" OR cytotoxicity OR biocompatibility OR "material release" OR "release kinetics" OR degradation OR inflammation OR regeneration OR angiogenesis OR mineralization OR "drug testing" OR "material testing" OR "host–material interaction" OR "host–pathogen interaction" OR "material–tissue interface")*.

To capture studies addressing computational and predictive approaches, an additional search was performed using the following string: *("organ-on-a-chip" OR "lab-on-a-chip" OR microfluidic* OR "microphysiological system*") AND ("artificial intelligence" OR "machine learning" OR "deep learning" OR "predictive model*" OR "image analysis" OR biosensor* OR "real-time monitoring" OR "automated analysis" OR "computational modeling") AND (dental OR dentistry OR oral OR biomaterial* OR biofilm OR "material–tissue interface")*.

Complete database-specific search strings, fields, limits, dates, and retrieval totals for the initial and update searches are provided in Supplementary Table S1. Truncation, phrase searching, and Boolean operators were adapted to the syntax of each information source.

2.5. Example PubMed search strategy

The following search strategy was adapted for PubMed/MEDLINE: *(("organ-on-a-chip"[Title/Abstract] OR "organs-on-chips"[Title/Abstract] OR "lab-on-a-chip"[Title/Abstract] OR microfluidic*[Title/Abstract] OR "microphysiological system*"[Title/Abstract] OR "biofilm-on-chip"[Title/Abstract] OR "tooth-on-a-chip"[Title/Abstract] OR "dentin-on-a-chip"[Title/Abstract] OR "pulp-on-a-chip"[Title/Abstract] OR "gingiva-on-a-chip"[Title/Abstract] OR "periodontal-on-a-chip"[Title/Abstract] OR "implant-on-a-chip"[Title/Abstract]) AND (dentistry[Title/Abstract] OR dental[Title/Abstract] OR tooth[Title/Abstract] OR dentin[Title/Abstract] OR pulp[Title/Abstract] OR "dental pulp"[Title/Abstract] OR odontoblast*[Title/Abstract] OR endodontic*[Title/Abstract] OR periodontal[Title/Abstract] OR periodontitis[Title/Abstract] OR gingiva[Title/Abstract] OR oral[Title/Abstract] OR "oral mucosa"[Title/Abstract] OR saliva[Title/Abstract] OR salivary[Title/Abstract] OR peri-implantitis[Title/Abstract] OR implant[Title/Abstract] OR craniofacial[Title/Abstract]) AND (biomaterial*[Title/Abstract] OR scaffold*[Title/Abstract] OR hydrogel*[Title/Abstract] OR adhesive*[Title/Abstract] OR resin[Title/Abstract] OR "calcium silicate"[Title/Abstract] OR bioceramic*[Title/Abstract] OR titanium[Title/Abstract] OR zirconia[Title/Abstract] OR cytotoxicity[Title/Abstract] OR biocompatibility[Title/Abstract] OR inflammation[Title/Abstract] OR regeneration[Title/Abstract] OR angiogenesis[Title/Abstract] OR mineralization[Title/Abstract] OR "drug testing"[Title/Abstract] OR "material testing"[Title/Abstract]))*.

Equivalent database-specific adaptations for Scopus, Web of Science Core Collection, ScienceDirect, Embase, and IEEE Xplore are presented in Supplementary Table S1.

2.6. Eligibility criteria

Studies were considered eligible when they reported, evaluated, or discussed microfluidic, LoC, OoC, flow-cell, or microphysiological systems with relevance to dental biomaterials, oral biology, craniofacial research, biofilms, or biomaterial–tissue interactions. Eligible studies included those addressing the design, fabrication, validation, or biological application of these platforms in dental, oral, pulpal, periodontal, gingival, salivary, peri-implant, or oral biofilm models. Studies investigating dental biomaterials, antimicrobial agents, regenerative scaffolds, adhesives, restorative materials, implant surfaces, tissue-engineered oral constructs, biosensors, real-time monitoring, AI, image analysis, or predictive modeling were also included when directly related to dynamic biomaterial evaluation. Original research articles, systematic reviews, scoping reviews, narrative reviews, methodological articles, and high-impact perspective papers were considered.

For synthesis, eligible sources were classified as: (1) original dental or oral microfluidic studies; or (2) dental/oral LoC or OoC reviews. General organ-on-a-chip, AI, engineering, and regulatory publications were retained only as contextual references and were not counted as included dental/oral evidence. Only original experimental studies contributed primary fabrication, fluidic, cellular, biomaterial, microbial, exposure, and endpoint data.

Studies were excluded if they lacked a dynamic microfluidic or microphysiological component; lacked direct dental, oral, craniofacial, biofilm, or biomaterial relevance; described engineering fabrication without biological application; used only conventional static assays; were not available in English; or were conference abstracts, editorials, commentaries, patents, theses, dissertations, non-peer-reviewed technical reports, or preprints without peer review.

2.7. Study selection process

All retrieved records were exported to reference management software, where duplicate entries were identified and removed before screening. The study selection process was conducted in three sequential stages. First, titles and abstracts were screened to identify records related to dental microfluidics, lab-on-a-chip systems, organ-on-a-chip platforms, oral biofilms, dental biomaterials, or biomaterial–tissue–biofilm interactions. Second, potentially eligible articles were reviewed in full to verify compliance with the eligibility criteria. Third, the included studies were grouped according to chip model, biological application, microfluidic configuration, dental or biomaterial relevance, and translational value.

Study selection was performed independently by two reviewers. Discrepancies were resolved by consensus. Record identification, screening, exclusion, and final inclusion were summarized in a PRISMA-style flow diagram (Fig. 1).

One principal exclusion reason was assigned to each full-text report. The exclusion categories and frequencies are reported in Fig. 1 and Section 3.1, and the citation-level disposition audit is provided in Supplementary Table S2.

2.8. Data extraction

Data were collected using a standardized extraction form to maintain consistency across the included studies. For each article, bibliographic information was recorded, including authorship, publication year, journal, and country of origin when reported. Study type was classified as original research, review, methodological article, or perspective paper.

Technical information was extracted regarding the microfluidic or microphysiological platform, including the chip model, chip material, and device configuration. Chip models were categorized as tooth-on-chip, dentin-on-chip, pulp-on-chip, periodontal-on-chip, gingiva-on-chip, biofilm-on-chip, implant-on-chip, or other relevant microphysiological systems. Chip materials included polydimethylsiloxane (PDMS), thermoplastics, hydrogels, glass, hybrid materials, or other reported substrates. Microfluidic designs were classified according to their architecture, including single-channel, dual-chamber, multichannel, serpentine, Y-mixer, gradient generator, central chamber, or

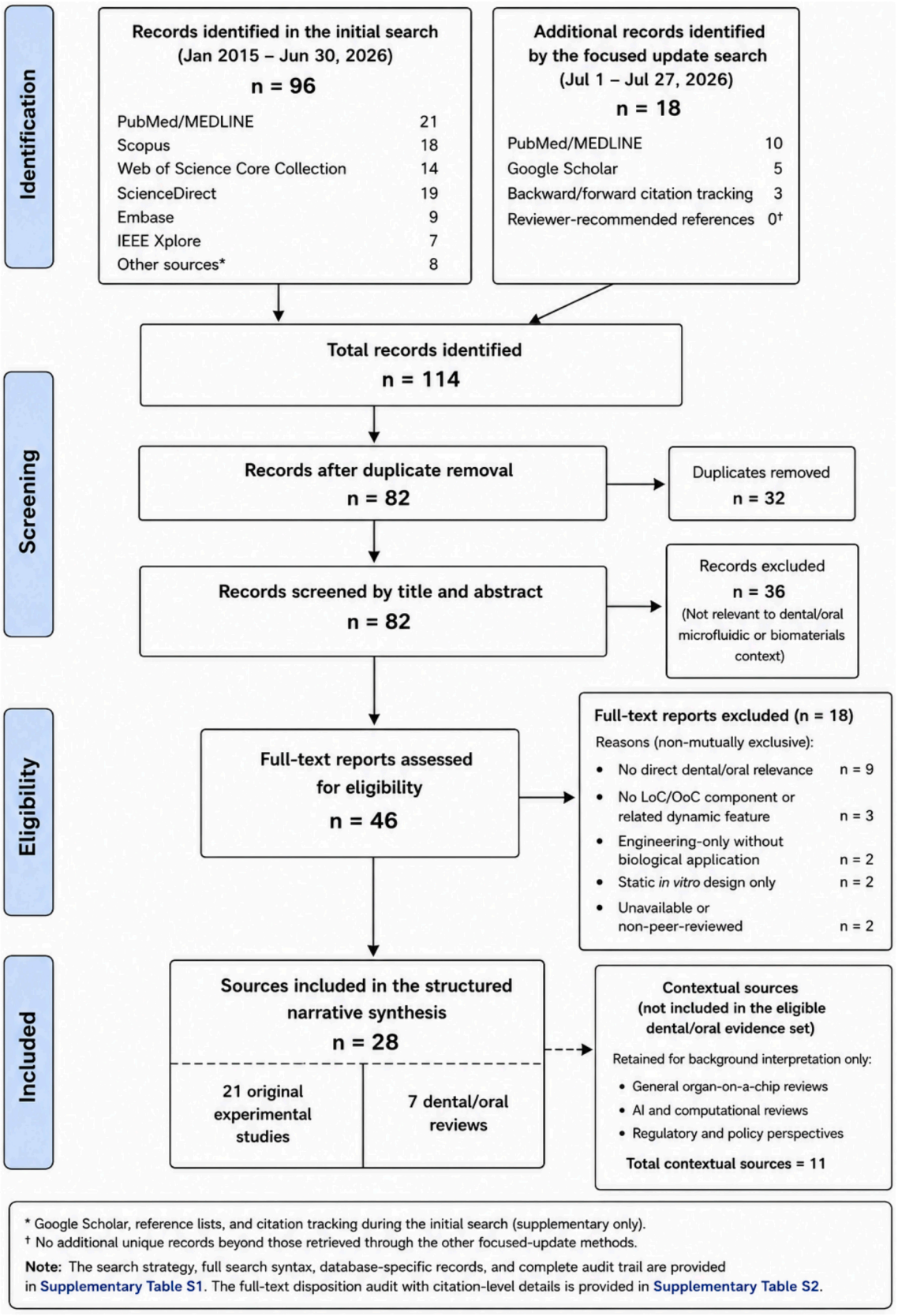


Fig. 1. PRISMA-style flow diagram of the study selection process. A total of 114 records were identified, including 96 from the initial search and 18 from the focused update. After removal of 32 duplicates, 82 records were screened; 36 were excluded at title/abstract level and 46 full-text reports were assessed. Eighteen full-text reports were excluded because they lacked direct dental/oral relevance ($n = 9$), lacked a LoC/OoC or related dynamic component ($n = 3$), were engineering-only without biological application ($n = 2$), used static designs only ($n = 2$), or were unavailable/non-peer-reviewed ($n = 2$). Twenty-eight sources were included: 21 original experimental studies and seven dental/oral reviews.

compartmentalized co-culture systems.

Biological and application-related information was also extracted, including the type of biological model, cell source, microbial system, extracellular matrix, dentin disk, scaffold, biomaterial, or implant-associated substrate used. Dental and biomaterial applications were categorized according to their primary purpose, including cytotoxicity testing, antimicrobial evaluation, inflammatory response, regenerative potential, tissue engineering, implant research, material release, and biomaterial–tissue–biofilm interaction analysis.

When reported, dynamic experimental parameters were collected, including flow rate, shear stress, concentration gradients, exposure time, perfusion mode, and culture duration. Analytical endpoints included cell viability, morphology, proliferation, cytokine expression, gene and protein expression, mineralization, biofilm biomass, bacterial viability, live imaging, fluorescence analysis, and real-time monitoring. Finally, translational relevance was assessed by extracting the clinical scenario modeled, predictive value, main limitations, and the presence of AI- or sensor-based integration, including image analysis, machine learning, biosensing, automated quantification, and predictive modeling.

Additional engineering and biological variables were recorded when available, including fabrication method, channel dimensions, barrier thickness, oxygenation, pH control, salivary simulation, material adsorption, microbial species, surface-area-to-volume relationship, sterility procedures, sensor calibration, replicate number, and comparison with static, animal, or clinical data. Parameters not reported in the original publications were identified as “not reported” and were not inferred.

The standardized data-extraction form is provided as Supplementary Table S3.

2.9. Quality appraisal and critical assessment

Because the original studies were methodologically heterogeneous, no single risk-of-bias tool was appropriate across all engineering and biological designs. A tailored reporting-completeness assessment was therefore used to describe whether key engineering, biological, analytical, comparator, and validation items were reported.

Original experimental studies were assessed according to the clarity of chip design and fabrication protocol, biological relevance of the model, appropriateness of the cell type or microbial system, description of dynamic parameters such as flow rate, shear stress, exposure time, and perfusion mode, presence of static control groups, reproducibility of experimental conditions, use of clinically relevant biomaterials or stimuli, validity of analytical endpoints, adequacy of statistical reporting, and translational relevance to dental or oral applications.

Each technical item was classified as reported, partially reported, or not reported. No global numerical score or high/moderate/low quality category was assigned because such labels could imply a formally validated risk-of-bias assessment. Review and perspective articles were not evaluated together with original experimental studies and were used only for contextual synthesis. The item-level assessment is provided in Supplementary Table S4.

2.10. Data synthesis

A quantitative meta-analysis was not conducted because the included studies differed substantially in design, chip configuration, biological model, biomaterial type, dynamic parameters, and analytical endpoints. Instead, the evidence was synthesized narratively and structured into ten thematic chapters: 1) Study selection; 2) Why dental biomaterials need lab-on-a-chip and organ-on-a-chip systems?; 3) Tooth-on-a-chip and Dentin–pulp-on-a-chip systems; 4) Periodontal-on-a-chip, Gingiva-on-a-chip, and Implant-on-a-chip systems; 5) Biofilm-on-a-chip models for antimicrobial dental biomaterials; 6) Integration of artificial intelligence with dental lab-on-a-chip platforms; 7) Proposed Dental Microfluidic Ecosystem Platform; 8) Reduction of animal models; 9) Future Directions; 10) Limitations.

The synthesis examined how each platform supported dynamic and human-relevant assessment of material–tissue–biofilm interactions. Biological relevance, technological maturity, biomaterial applicability, control of microfluidic variables, translational value, limitations, and integration into future dental biomaterial qualification and analytical workflows were considered. Original experimental studies provided the technical and biological evidence, whereas reviews, AI perspectives, and regulatory publications were used only for contextual interpretation.

3. Results

3.1. Study selection

The initial search identified 96 records. The focused update search identified 18 additional unique records, producing 114 records before deduplication. After removal of 32 duplicates, 82 records underwent title and abstract screening. The overall study selection process is summarized in the PRISMA-style flow diagram shown in Fig. 1.

After duplicate removal, 82 records were screened by title and abstract, and 36 were excluded because they were outside the dental/oral scope or did not describe a potentially eligible dynamic microfluidic system.

Forty-six full-text reports were assessed. Eighteen were excluded: no direct dental, oral, craniofacial, biofilm, or dental-biomaterial relevance ($n = 9$); no LoC, OoC, flow-cell, or microphysiological component ($n = 3$); engineering-only focus without biological application ($n = 2$); static *in vitro* design without controlled flow or compartmentalization ($n = 2$); and unavailable or non-peer-reviewed publication type ($n = 2$). General OoC, AI, and regulatory papers excluded from the mapped dental/oral evidence were retained only when needed for contextual discussion.

Twenty-eight sources were included in the structured narrative synthesis: 21 original dental/oral microfluidic studies and seven dental/oral reviews. The original studies encompassed tooth and dentin–pulp interfaces, oral mucosa and gingival barriers, periodontal and bone–vascular models, dental pulp angiogenesis, peri-implant interfaces, and dynamic host–microbe systems.

General OoC/AI and regulatory publications were retained only as contextual references and were not counted as eligible dental/oral evidence.

The technical characteristics of the 21 original experimental studies are summarized in Tables 1A and 1B. The 28 eligible sources and their specific role in the review are classified in Table 2. A cross-model comparison of technical feasibility, reproducibility, relative cost, and experimental throughput is provided in Table 3.

3.2. Why dental biomaterials need lab-on-a-chip and organ-on-a-chip systems?

The performance of dental biomaterials is shaped by continuous interactions with host tissues, oral fluids, and microbial communities. Although static *in vitro* assays remain useful for preliminary screening, they usually expose cells to material extracts under simplified conditions and cannot capture processes such as fluid transport, transdentinal diffusion, bacterial adhesion under flow, or host–microbe–material crosstalk.

This gap is especially relevant for resin-based materials, calcium silicate cements, bioceramic sealers, antimicrobial hydrogels, nanomaterials, and implant coatings. These materials may release monomers, ions, nanoparticles, degradation products, or antimicrobial compounds over time, and their biological effects depend not only on composition but also on release kinetics, concentration gradients, and the presence of tissue barriers.

Microfluidic platforms provide a way to control these variables with greater spatial and temporal precision. The tooth-on-a-chip model reported by França et al. reproduced key features of the

Table 1A
Engineering and fluidic characteristics of original dental and oral microfluidic studies.

Study/ model	Chip material	Architecture	Flow/ perfusion	Shear stress
França et al. (2020) [9]	PDMS/glass	Two chambers separated by human dentin	Perfusion/ diffusion; rate NR	NR
Rahimi et al. (2018) [26]	PDMS/glass	Oral epithelial and stromal microchannels	Surface-tension-driven; rate NR	NR
Niu et al. (2019) [27]	Microfabricated polymer; NR	Microchannels approximating dentinal tubules (~2 μm)	No continuous perfusion reported	NR
Ly et al. (2021) [28]	PDMS/glass	Three-channel oral mucosa device	Estimated injection 1–4 μL/min; passive culture	NR
Rodrigues et al. (2021) [29]	PDMS/glass with dentin	Biomaterial/biofilm and pulp compartments separated by dentin	Dynamic transdentinal exposure; rate NR	NR
Hu et al. (2022) [31]	Tooth chip plus engineered gingival equivalents	Transdentinal and gingival exposure models	Rate NR	NR
Zhang et al. (2024) [10]	Microfluidic device with GelMA	Three-channel 3D SCAPs–GelMA construct	Dynamic culture; rate NR	NR
Cordiale et al. (2026) [11]	Microfluidic device; substrate NR	Pulp and neural compartments connected by microgrooves	Diffusion-based transport; rate NR	NR
Svanberg et al. (2026) [40]	Microfluidic fibrin-based angiogenesis device	Dental-pulp and endothelial angiogenic compartments	Gradient-driven; rate NR	NR
Álamo et al. (2026) [41]	Artificial pulp chamber system	0.35-mm dentin discs under simulated pulpal pressure	Hydraulic pressure; flow rate NR	NR
Jin et al. (2022) [30]	PDMS with 10-μm membrane	Perpendicular epithelial and capillary channels	Perfusion; rate NR	NR
Makkar et al. (2023) [32]	PDMS/hydrogel	Horizontal channels and central connective-tissue chamber	Hydrostatic crevicular/ interstitial flow	NR
Gard et al. (2023) [33]	Membrane-bilayer PREDICT96	Two channels separated by 1-μm membrane; 96 devices	10 μL/min recirculating flow	NR
Muniraj et al. (2023) [34]	Vertically stacked thermoplastic/ millifluidic device	Full-thickness gingival equivalent at air–liquid interface	Active perfusion; exact rate NR	NR
Mishra et al. (2023) [35]	Microfluidic perfusion device	PDLSCs spheroid chamber	1.2 and 7.2 μL/min	59 and 360 μPa
Svanberg et al. (2024) [36]	Microfluidic 3-channel device	Three parallel channels separated by micropillars	Perfused; rate NR	NR
Hu et al. (2025) [12]	PDMS 10:1 bonded to glass	Four channels; 150-μm depth; central gel channels 1.3 mm	Reservoir-mediated exchange; rate NR	NR
Chen et al. (2025) [39]	Microfluidic bone–vessel chip	Adjacent bone and vascular compartments	Perfusion; rate NR	NR
Dhall et al. (2022) [13]	PDMS/glass with resin and titanium blocks	Separated resin–keratinocyte and titanium–fibroblast chambers	0.3 μL/min/ inlet	0.009 dyn/ cm^2
Machla et al. (2025) [37]	Additively manufactured microfluidic device	Two interconnected chambers for oral mucosa analogue	Perfusion; rate NR	NR
Surrency et al. (2025) [38]	3D peri-implant microfluidic platform	Epithelial–mucosal barrier adjacent to implant material	Perfusion; rate NR	NR

PDMS, polydimethylsiloxane, SCAPs, stem cells form the apical papilla, PDLSCs, periodontal ligament stem cells
NR, not reported in the original publication or not available from the current extraction.

pulp–dentin–biomaterial interface and allowed live-cell imaging of dental pulp cell responses to restorative materials [9]. In that system, dental materials induced cytotoxic effects under both on-chip and off-chip conditions; however, cells maintained higher metabolic activity in the microfluidic environment, suggesting that dynamic culture conditions may better support biomaterial testing than conventional static models.

Recent dental reviews indicate that OoC systems may support antibacterial testing, biomaterial evaluation, inflammatory-disease modeling, and reduction of reliance on animal experimentation [2–4,20,21,42]. Building on this evidence, the conceptual Modular Dental Microfluidic Ecosystem Platform extends beyond individual tooth, dentin, pulp, gingival, periodontal, implant, or biofilm models by integrating biomaterial release, concentration gradients, host-cell responses, microbial challenge, biosensing, and AI-assisted analysis. Because the integrated platform has not been fabricated or experimentally validated, it should be interpreted as a conceptual framework rather than as an established experimental platform.

3.3. Tooth-on-a-chip and dentin–pulp-on-a-chip platforms

The dentin–pulp complex is a critical interface for the evaluation of restorative and regenerative materials. It includes mineralized dentin, dentinal tubules, odontoblast-like cells, dental pulp stem cells, vascular components, neural elements, immune mediators, and extracellular matrix. Conventional models mainly isolate these components, whereas tooth-on-a-chip systems allow their partial integration under controlled microfluidic conditions.

Early dental microfluidic studies established complementary approaches to the dentin–pulp interface. Rahimi et al. [26] and Ly et al. [28] demonstrated that oral mucosa chips can reveal layer-specific responses to bacteria and dental monomers, whereas Niu et al. [27] used microchannels to study odontoblast process formation. França et al. [9] introduced a two-compartment tooth-on-chip separated by human dentin, allowing live monitoring of pulp-cell responses to restorative-material exposure.

Rodrigues et al. [29] subsequently combined a pulp–dentin interface, bioactive cements, and *Streptococcus mutans* to examine cell response, pH, TGF-β release, and biofilm behavior. Hu et al. [31] used tooth-on-chip and gingival equivalents to characterize silver diamine fluoride cytotoxicity in tissue-specific contexts. Zhang et al. [10] integrated a GelMA-based three-dimensional stem cells from the apical papilla (SCAPs) construct for regenerative material screening.

More recent systems increased biological or translational complexity. Cordiale et al. [11] incorporated odontoblast-like, vascular, stem-cell, and trigeminal-neural compartments. Svanberg et al. [40]

Table 1B
Biological components, challenges, comparators, and validation evidence.

Study/model	Biological barrier/interface	Biomaterial or challenge	Comparator	Validation evidence and main limitation
França et al. (2020) [9]	Dentin barrier; SCAPs/pulp cells	HEMA, phosphoric acid, adhesive	On-chip *vs* off-chip	Live imaging, viability, gelatinolysis; limited immune/vascular complexity
Rahimi et al. (2018) [26]	Oral keratinocyte–fibroblast interface	Dental materials and bacteria	Layer-specific controls	Layer-specific viability and inflammatory response; limited long-term complexity
Niu et al. (2019) [27]	Odontoblast-like cells in microchannels	Microtopographic stimulation	Conventional culture	Odontoblast process formation; limited material testing
Ly et al. (2021) [28]	Keratinocytes and fibroblasts in collagen	HEMA 1.56–25 mM	Well-plate monoculture	Greater sensitivity to monomer exposure; no immune/vascular cells
Rodrigues et al. (2021) [29]	Dentin–pulp interface and *S. mutans*	ProRoot MTA, Biodentine, TheraCal LC	Static/off-chip comparison	Viability, pH, TGF-β and biofilm; incomplete fluidic standardization
Hu et al. (2022) [31]	Dentin barrier and gingival tissue equivalent	Silver diamine fluoride	Direct-cell/tissue-equivalent comparison	Tissue-specific cytotoxicity; incomplete hydraulic reporting
Zhang et al. (2024) [10]	SCAPs in dentin-like GelMA	Regenerative material screening	Conventional culture comparator	Viability and odontogenic differentiation; simplified dentin architecture
Cordiale et al. (2026) [11]	hDPSCs, odontoblast-like, endothelial and neural cells	Physiology/pathology; future material testing	Internal multicellular validation	Vascular, neural and odontogenic readouts; high complexity
Svanberg et al. (2026) [40]	Dental pulp cells and endothelial cells	Paclitaxel, Limantrafin; biomaterial-testing potential	Dose and material controls	Angiogenic sprouting and cytotoxicity; single-laboratory validation
Álamo et al. (2026) [41]	Sound/caries-affected dentin; MDPC-23 and HDPC in collagen	Universal adhesives, self-etch/etch-and-rinse	Material-free and dentin-condition controls	24-h transdentinal cytotoxicity; requires broader validation
Jin et al. (2022) [30]	Gingival epithelial–endothelial barrier	LPS, TNF-α, anti-inflammatory treatment	Untreated controls	TEER/permeability and inflammatory response; simplified tissue layers
Makkar et al. (2023) [32]	Gingival connective-tissue and microbiome interface	5-FU and host–microbiome challenge	Static/animal contextual comparison	Transport and mucositis modeling; external replication absent
Gard et al. (2023) [33]	Keratinocytes, fibroblasts and endothelial cells	TNF-α/IL-1β and p38 inhibitor	Multiple controls and experiments	TEER, cytokines, 28–32 d culture; donor diversity limited
Muniraj et al. (2023) [34]	Keratinocyte–fibroblast fibrin matrix	Oral-care/material exposure	Flow *vs* static	Improved maturation and host–material response; hydrodynamics incompletely reported
Mishra et al. (2023) [35]	PDLSCs spheroids	Osteogenic culture	Static, low- and high-flow	Viability and osteodifferentiation; no direct material/microbial challenge
Svanberg et al. (2024) [36]	PDL cells and endothelial cells in fibrin	Physiological/pathological PDL modeling	Static/disease controls	Vascular network and tissue markers; material validation pending
Hu et al. (2025) [12]	Epithelium, fibroblasts, HUVECs, THP-1	*P. gingivalis* and *A. muciniphila*	Healthy/disease microbial conditions	TEER, permeability, cytokines >12 d; continuous shear not quantified
Chen et al. (2025) [39]	hBMSCs and HUVEC barrier	LPS/TNF-α periodontal cues	Physiological *vs* inflammatory conditions	Permeability and osteogenesis 7–21 d; indirect dental-material relevance
Dhall et al. (2022) [13]	Gingival keratinocyte and fibroblast interfaces	*S. mutans* and photobiomodulation	Flask and untreated controls	CFD, cell loss and therapy response; simplified biofilm/immune model
Machla et al. (2025) [37]	Oral mucosa analogue	Host–material applications	Static/biocompatibility controls	Fabrication and short-term viability; limited disease validation
Surrency et al. (2025) [38]	Peri-implant epithelium/mucosa and titanium	Host–bacteria–biomaterial challenge	Unchallenged controls	Barrier-function changes; needs interlaboratory and broader biofilm validation

Table 2
Classification and use of the evidence.

Evidence category	References	Use in this review	Technical parameters extracted	Principal contribution	Main limitation
Original experimental studies ($n = 21$)	França [9]; Zhang [10]; Cordiale [11]; Hu [12]; Dhall [13]; Rahimi [26]; Niu [27]; Ly [28]; Rodrigues [29]; Jin [30]; Hu [31]; Makkar [32]; Gard [33]; Muniraj [34]; Mishra [35]; Svanberg [36]; Machla [37]; Surrency [38]; Chen [39]; Svanberg [40]; Álamo [41]	Primary evidence	Fabrication, geometry, flow, cells, materials/microbes, exposure, endpoints and comparators	Defines current experimental capabilities and limitations	Heterogeneous reporting and predominantly single-laboratory validation
Dental/oral reviews ($n = 7$)	Wadan [1]; Huang [2]; Pierfelice [3]; Sriram and Makkar [4]; Mitsiadis and Pagella [20]; Ardila et al. [21]; Zhong et al. [42]	Contextual mapping	No primary technical values extracted	Maps dental/oral OoC applications, gaps, and future directions	Secondary evidence dependent on a small and rapidly changing primary literature
General AI/OoC context	Pousti [14]; Deng [15]; Gangwal and Lavecchia [16]; An et al. [18]; Li et al. [22]; Liu et al. [23]	Context only; not counted in $n = 28$	No dental-specific device parameters	Supports discussion of biofilm flow cells, AI, deep learning, and hydrogel modules	Not direct dental predictive or fabrication validation
Regulatory/NAM context	Zushin et al. [17]; Gerke et al. [19]; Lei et al. [24]; U.S. Congress [25]; ISO 10993-5 [43]; ISO 10993-12 [44]	Context only; not counted in n = 28	Not applicable	Supports cautious discussion of qualification, NAMs, and regulatory context	Does not establish validation of dental OoC platforms

developed a microfluidic dental-pulp angiogenesis model for drug and biomaterial testing. Álamo et al. [41] used a microphysiological artificial pulp chamber with 0.35-mm sound or caries-affected dentin under simulated pulpal pressure to assess trans-dentinal adhesive cytotoxicity.

Together, these studies support applications in adhesives, resin monomers, calcium-silicate cements, bioceramics, silver diamine

Table 3
Cross-model comparison of technical feasibility, reproducibility, cost, and experimental throughput.

Model	Fabrication complexity	Relative cost*	Throughput	Reproducibility evidence	Static/conventional comparator	Main limitation	Representative references
Tooth/ dentin–pulp	Moderate–high	High	Low	Within-study only; no interlaboratory validation	On-chip/off-chip, dentin controls, or artificial pulp chambers	Dentin variability, sealing, hydraulic standardization	[9–11,27,29,31,40,41]
Oral mucosa/ gingiva	Moderate–high	Moderate–high	Low to high (PREDICT96)	Barrier and long-term repeatability within studies	Static, matrix-only, untreated, or inflammatory controls	Donor effects, maturation, oxygen and flow reporting	[12,26,28,30,32–34,37]
Periodontal/ PDL/ bone–vessel	High	High	Low–moderate	Mostly single-study validation	Static/flow and healthy/ inflammatory controls	Vascular stability, immune and material integration	[35,36,39]
Peri-implant	High	High	Low	Single-laboratory fluidic and biological validation	Flask, unchallenged, or material controls	Multispecies biofilm, immune complexity, external replication	[13,38]
Biofilm-enabled oral chips	Moderate–high	Moderate	Moderate	Model-specific; broader flow-cell maturity	Static microbial or material controls vary	Host integration, anaerobiosis, salivary pellicle	[12–14,26,29,32,38]
Conceptual Modular Dental Microfluidic Ecosystem	Very high	Undetermined	Undetermined	None; conceptual framework only	Not applicable	Compatibility and staged validation of all modules	Present review; [1,15,16,22,23]

* Relative cost is an evidence-informed qualitative estimate based on fabrication requirements, biological complexity, specialized equipment, personnel, and culture duration.

fluoride, pulp-capping agents, hydrogels, regenerative scaffolds, and angiogenesis-modulating therapies.

Comparison remains constrained by differences in dentin thickness and orientation, hydraulic conditions, channel geometry, cell source, extracellular matrix, material volume, curing procedure, exposure duration, and comparator selection. Future studies should report these variables consistently and include ISO-aligned static controls and independent replication whenever feasible.

These developments suggest that dentin–pulp-on-a-chip systems could become highly relevant for evaluating adhesives, calcium silicate cements, bioceramic sealers, silver diamine fluoride, injectable hydrogels, pulp-capping materials, and regenerative endodontic scaffolds. Fig. 2 represents a conceptual microfluidic device for next-generation dynamic evaluation of dental biomaterials at the dentin-pulp interface.

Despite these advances, comparison among dentin–pulp platforms remains limited by differences in dentin thickness, tubule orientation, hydraulic conditions, cell source, extracellular matrix, material volume, and exposure duration. Future studies should report these parameters consistently and include parallel static controls whenever possible.

3.4. *Periodontal-on-a-chip, gingiva-on-a-chip, and implant-on-a-chip systems*

Periodontal and peri-implant tissues are complex biological interfaces where host cells, microbial biofilms, inflammatory mediators, and biomaterials interact continuously. Periodontal disease is driven by dysbiosis and host immune responses that contribute to the destruction of gingiva, periodontal ligament, cementum, and alveolar bone. Microfluidic periodontal platforms are therefore particularly relevant for studying host–microbe and host–material interactions.

Periodontal and oral-mucosal microfluidics now encompass several distinct architectures. Jin et al. [30] developed an epithelium–capillary interface chip for inflammatory and drug-response studies. Makkar et al. [32] modeled gingival crevicular and interstitial flow, and Gard et al. [33] demonstrated a 96-device platform with recirculating flow, barrier monitoring, and culture for approximately one month. Muniraj et al. [34] reconstructed full-thickness gingival equivalents under perfusion and an air–liquid interface.

Regenerative and disease-oriented periodontal models include flow-conditioned periodontal-ligament stem-cell spheroids [35], a vascularized periodontal-ligament-on-chip [36], a multicellular gum-on-chip with epithelial, stromal, endothelial, immune, and microbial components [12], and a bone–vessel interface used to model vascular permeability, osteogenic maturation, and inflammatory periodontal cues [39].

Peri-implant and oral-mucosal systems have also advanced. Dhall et al. [13] integrated resin–keratinocyte and titanium–fibroblast interfaces with *Streptococcus mutans* challenge. Machla et al. [37] developed an additively manufactured oral-mucosa chip, while Surrency et al. [38] reported a three-dimensional peri-implant epi-mucosa model for host–bacteria–biomaterial interactions.

These models are directly relevant for evaluating titanium surface modifications, zirconia implants, antimicrobial coatings, nanostructured implant surfaces, photobiomodulation strategies, and anti-inflammatory or antibacterial biomaterials. Based on these applications, Fig. 3 proposes a next-generation periodontal–gingiva–implant-on-a-chip platform designed to integrate multispecies biofilm formation, gingival epithelial barrier function, connective tissue response, periodontal ligament fibroblast behavior, vascular perfusion, implant surface interactions, and immune/inflammatory signaling under dynamic microfluidic conditions.

Current periodontal, gingival, and implant models differ substantially in channel architecture, perfusion mode, epithelial maturation, immune-cell inclusion, microbial complexity, and material integration. Their translational value will depend on standardized reporting, long-term barrier validation, multispecies biofilms, and interlaboratory reproducibility.

3.5. *Biofilm-on-a-chip models for antimicrobial dental biomaterials*

Oral biofilms are dynamic communities shaped by nutrient delivery, flow, shear, oxygen and pH gradients, salivary conditioning, surface chemistry, and interactions with host tissues. Static antimicrobial assays cannot reproduce this coupled transport and community behavior.

Biofilm and host–microbe components have been incorporated into oral mucosa chips [26], pulp–dentin models [29], gingival crevice and gum platforms [12,32], implant systems [13,38], and broader microfluidic flow-cell workflows [14]. These models permit time-resolved analysis of adhesion, barrier disruption, antimicrobial penetration,

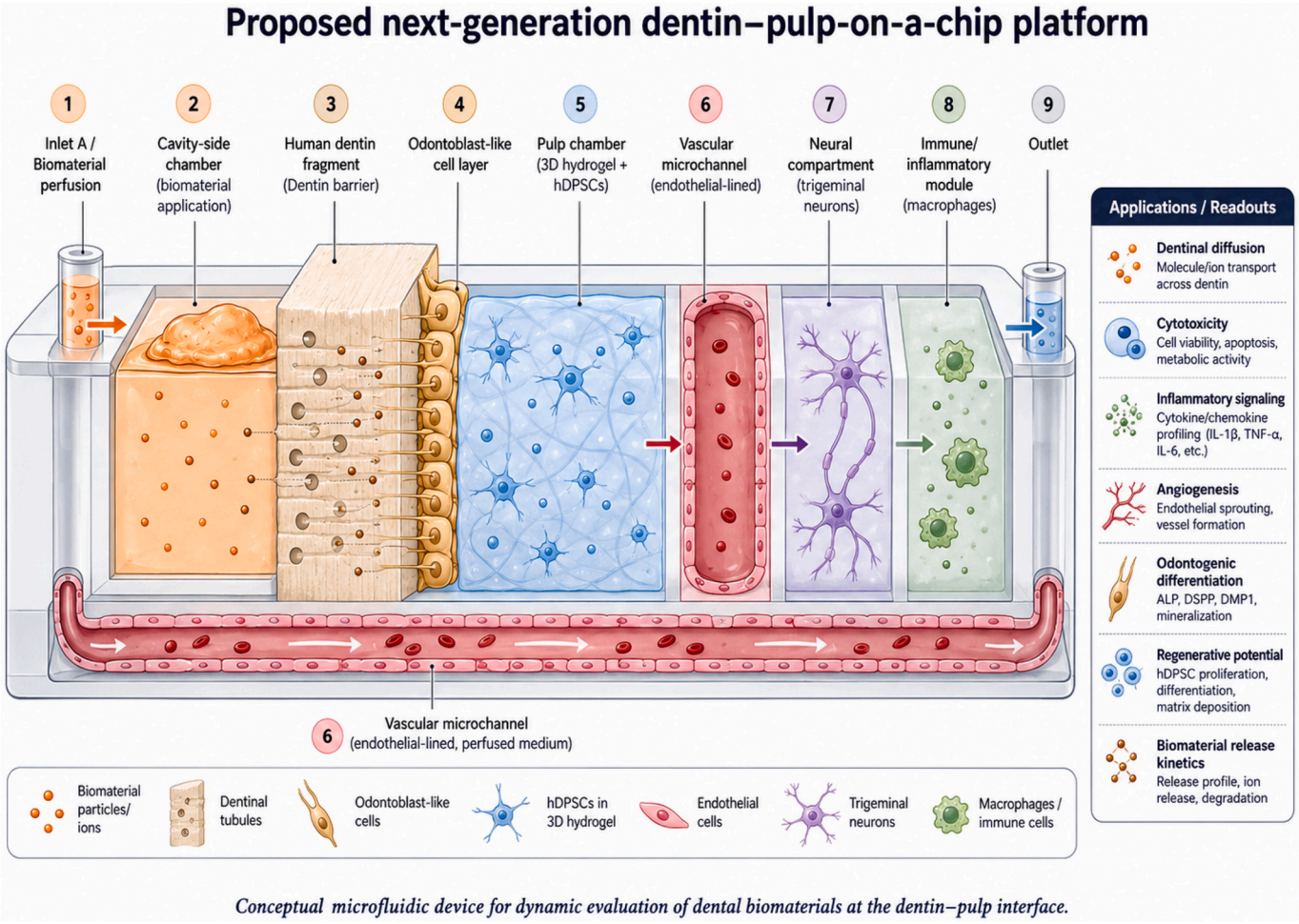


Fig. 2. Conceptual next-generation dentin–pulp-on-a-chip platform. The schematic illustrates a microfluidic model for evaluating biomaterial transport and biological responses across the dentin–pulp interface. Principal components include a biomaterial chamber, dentin barrier, odontoblast-like layer, pulp-cell compartment, and vascular, neural, and inflammatory modules. The figure is conceptual, not to scale, and does not represent a fabricated or experimentally validated device. The figure was conceptually based on previously reported tooth-on-a-chip, dentin-on-a-chip, and advanced tooth-on-chip/dental pulp-on-chip platforms [9–11], [29,31,40,41].

biomass, viability, cytokine signaling, and material–biofilm interactions under controlled exposure.

For dental applications, these systems are well suited for evaluating chlorhexidine, sodium hypochlorite, calcium silicate materials, nanoparticles, antimicrobial hydrogels, bioactive glasses, plant-derived compounds, and implant coatings. They can also be adapted to multispecies biofilms representative of cariogenic, endodontic, periodontal, and peri-implant infections. Building on these applications, Fig. 4 presents a next-generation biofilm-on-a-chip concept that integrates salivary conditioning, microbial adhesion, biofilm maturation, antimicrobial exposure, detachment and recovery, host-interface response, and physicochemical monitoring under controlled microfluidic flow. This platform is proposed as a dynamic model to assess antimicrobial penetration, biofilm viability, regrowth capacity, inflammatory response, and the antibiofilm performance of dental biomaterials.

Although biofilm-on-chip models provide controlled shear, nutrient delivery, and real-time visualization, most dental applications still use simplified microbial communities. Future studies should incorporate salivary conditioning, anaerobic or oxygen-gradient control, clinically relevant multispecies biofilms, host-tissue interfaces, and standardized antimicrobial comparators.

To facilitate cross-model comparison, Table 3 summarizes fabrication complexity, relative cost, throughput, reproducibility evidence, conventional comparators, limitations, and representative references. Cost categories are qualitative estimates rather than formal economic analyses.

3.6. *Integration of artificial intelligence with dental lab-on-a-chip platforms*

The integration of AI into OoC systems opens an important avenue for dental biomaterials research, particularly as microfluidic platforms generate increasingly complex and multimodal datasets. Time-lapse microscopy, fluorescence intensity, cell morphology, biofilm architecture, cytokine profiles, pH shifts, oxygen gradients, and sensor-derived signals can be difficult to interpret using conventional endpoint analysis alone. AI-based approaches may help extract patterns from these high-dimensional outputs and translate them into biologically meaningful predictions.

Deng et al. [15] described the convergence between OoC technologies and AI in drug evaluation, highlighting the role of AI in image analysis, data integration, prediction of biological responses, and interpretation of complex microphysiological datasets. Li et al. [22] further reviewed the integration of deep-learning methods with OoC systems, highlighting their potential for automated image analysis, high-dimensional data processing, and interpretation of complex microphysiological outputs. In parallel, recent discussions in preclinical

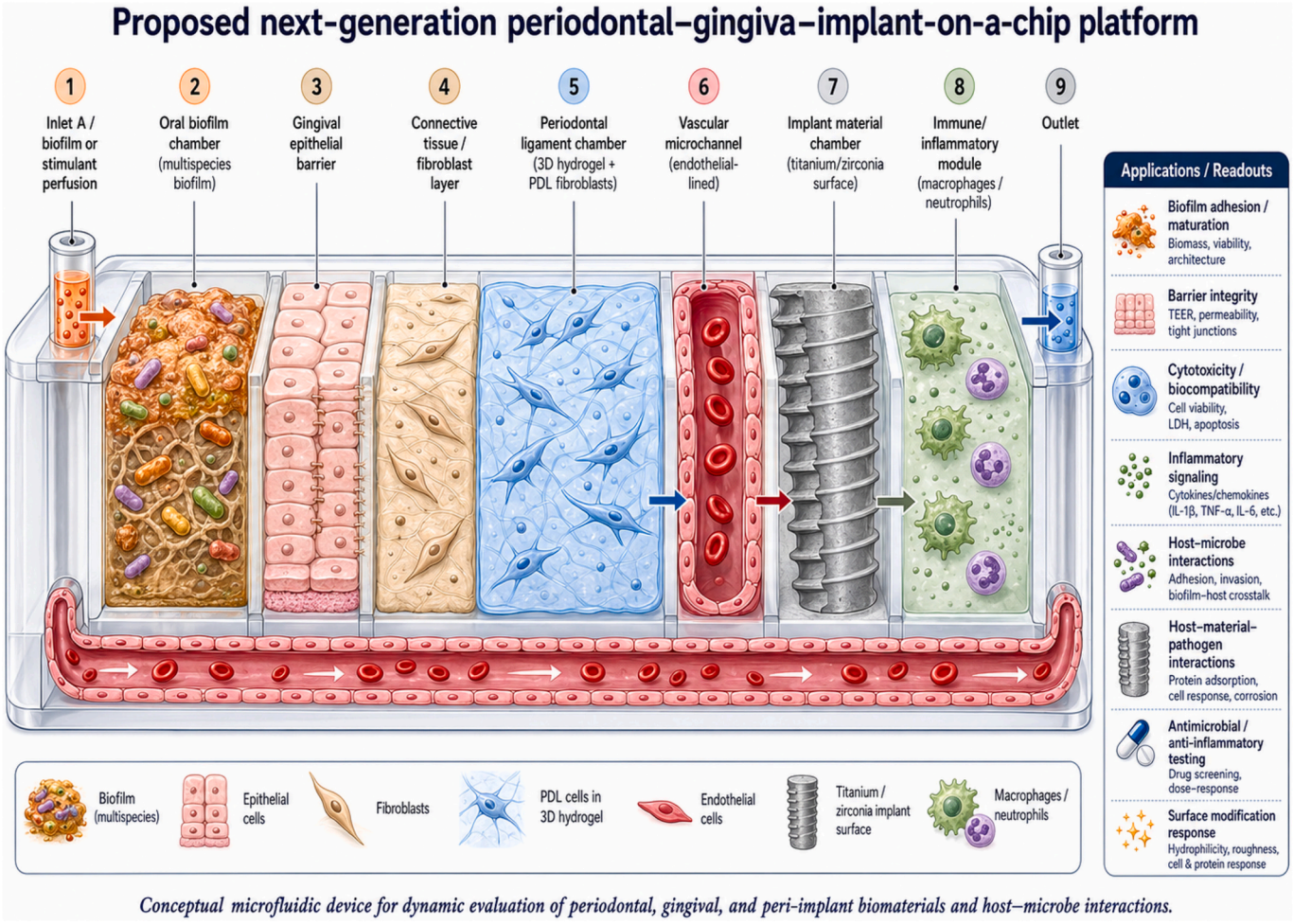


Fig. 3. Conceptual periodontal–gingiva–implant-on-a-chip platform. The schematic illustrates a multicompartment model for investigating dynamic host–microbe–material interactions in periodontal and peri-implant environments. Principal components include an oral biofilm chamber, gingival epithelial and connective-tissue layers, periodontal ligament compartment, vascular channel, immune module, and implant surface. The figure is conceptual, not to scale, and has not been fabricated or experimentally validated. The figure was conceptually inspired by periodontal microfluidic systems, gum-on-a-chip models, and dental implant-on-a-chip platforms [4,12,13].

research suggest that AI-enhanced organ-on-a-chip systems and digital twins may improve predictive modeling, reduce dependence on animal experimentation, and support more individualized experimental designs [16].

None of the original dental or oral microfluidic studies included in this review used AI or machine learning for externally validated predictive analysis. Consequently, the current evidence does not permit a quantitative conclusion that AI-assisted analysis is superior to conventional endpoint assays. The applications described below should therefore be interpreted as future opportunities derived primarily from the broader OoC literature.

In dental biomaterials research, these tools could be applied to automated dental pulp cell counting, quantification of odontoblast-like morphology, segmentation of biofilm biomass, analysis of bacterial viability under flow, exploratory assessment of biomaterial-associated cytotoxicity, detection of inflammatory phenotypes, classification of scaffold–cell interactions, optimization of release kinetics, and hypothesis-generating prioritization of biomaterials using patient-derived cells. In this context, AI could potentially serve as an analytical layer for automated segmentation, pattern recognition, multimodal data integration, and experimental optimization. However, predictive implementation will require adequately sized annotated datasets, independent ground-truth labels, locked analytical models, external validation, calibration assessment, bias analysis, and comparison with conventional endpoint assays. Until these requirements are met, AI integration in dental microfluidic systems should be considered exploratory rather than predictive.

3.7. *Proposed dental Microfluidic Ecosystem Platform: a future perspective*

The following platform is a conceptual future framework derived from the capabilities and limitations identified in the reviewed literature. It has not been fabricated, experimentally validated, or compared with standardized dental biomaterial assays. Therefore, the proposed modules should not be interpreted as an experimentally executable device in their present form. Based on current evidence, we propose a modular Dental Microfluidic Ecosystem Platform composed of four integrated modules:

Release module: A serpentine microfluidic channel could be used to evaluate the time-dependent release of ions, monomers, nanoparticles, antimicrobial agents, degradation products, or bioactive compounds from dental biomaterials.

Gradient module: A Y-mixer or concentration-gradient generator could reproduce dose-dependent exposure conditions, allowing dynamic evaluation of cytotoxicity, antimicrobial activity, inflammation, differentiation, or mineralization.

Biological response module: A central biological chamber could

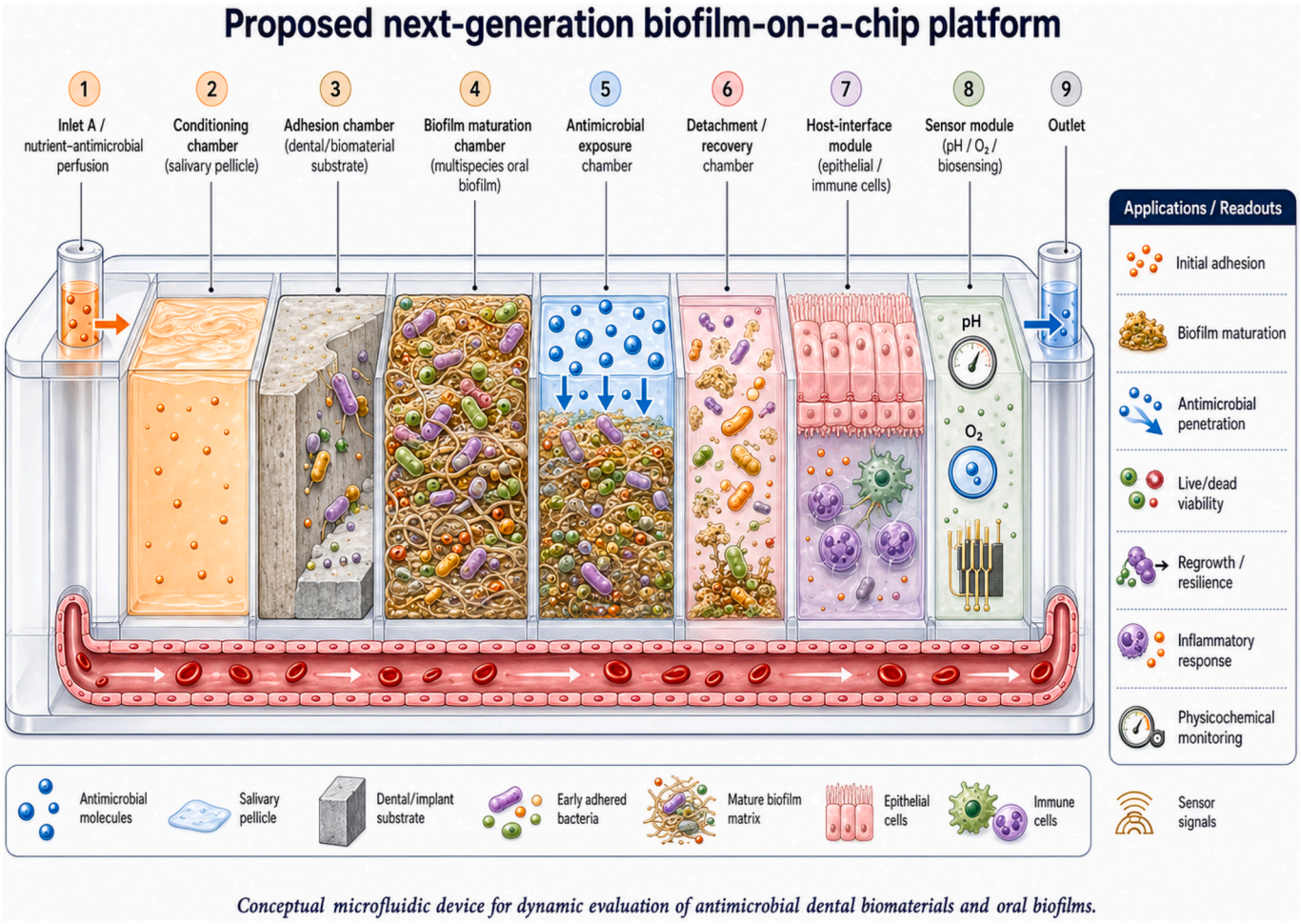


Fig. 4. Conceptual biofilm-on-a-chip platform for antimicrobial dental biomaterial evaluation. The schematic illustrates dynamic assessment of microbial adhesion, biofilm maturation, antimicrobial exposure, detachment, and recovery under controlled flow. Principal components include salivary conditioning, dental or biomaterial substrates, a multispecies biofilm chamber, antimicrobial exposure and recovery regions, a host-cell interface, and physicochemical monitoring. The figure is conceptual, not to scale, and experimentally unvalidated. The figure was conceptually inspired by microfluidic biofilm flow-cell systems [14].

integrate dental pulp cells, periodontal ligament fibroblasts, gingival epithelial cells, endothelial cells, immune cells, dentin disks, titanium surfaces, hydrogels, scaffolds, or biofilms. Hydrogel microspheres could provide tunable three-dimensional microenvironments for cell encapsulation, controlled biomolecule delivery, and modular integration within OoC systems [23].

AI-assisted analytical module: An AI module could process real-time imaging, fluorescence signals, cell morphology, biofilm architecture, and biochemical outputs to support exploratory classification, quantitative analysis, and hypothesis generation regarding biomaterial performance.

Future fabrication would require definition of substrate material, channel dimensions, chamber volume, surface-area-to-volume ratio, connection and pumping strategy, fluidic resistance, shear-stress range, oxygen and pH control, sterility, biofilm containment, sensor calibration, and material-adsorption behavior. Validation should proceed stepwise, beginning with individual modules, followed by fluidic and analytical qualification, biological repeatability, comparison with static ISO-aligned assays, and finally interlaboratory assessment.

The feasibility of integrating all modules into a single platform remains uncertain because the flow, oxygenation, sterility, and culture requirements of host cells and oral biofilms may be incompatible. A modular or sequential configuration may therefore be more realistic than a fully integrated device.

This modular system would allow dental biomaterials to be evaluated under dynamic, multicellular, microbiologically relevant, and computationally interpretable conditions. As illustrated in Fig. 5, the proposed Dental Microfluidic Ecosystem Platform integrates biomaterial input, release kinetics assessment, concentration-gradient generation, biological response modeling, microbial challenge, biosensor-based monitoring, AI-assisted exploratory analysis, and effluent collection within a single conceptual microfluidic workflow. Such a platform aligns with recent calls for high-fidelity oral microphysiological systems that integrate microfluidics, advanced biomaterials, nanosensors, and real-time monitoring [1].

To facilitate experimental translation, the full ecosystem platform should be implemented through a modular strategy rather than as a single fully integrated device in the initial stage. Accordingly, Fig. 6A–D presents four conceptual modular configurations derived from the proposed ecosystem. These configurations illustrate potential compartmental arrangements but do not represent fabricated, optimized, or experimentally validated systems. Fig. 6A shows a dentin–pulp-on-a-chip configuration for evaluating dentinal diffusion, pulp cell response, odontogenic differentiation, and biomaterial release across a dentin barrier. Fig. 6B presents a gingiva–biofilm-on-a-chip model designed to study epithelial barrier integrity, multispecies biofilm formation, inflammatory signaling, and host–microbe interactions under perfusion. Fig. 6C illustrates a conceptual implant–biofilm–fibroblast-on-a-chip configuration for analyzing peri-implant host–material–pathogen interactions, implant surface biocompatibility, fibroblast viability,

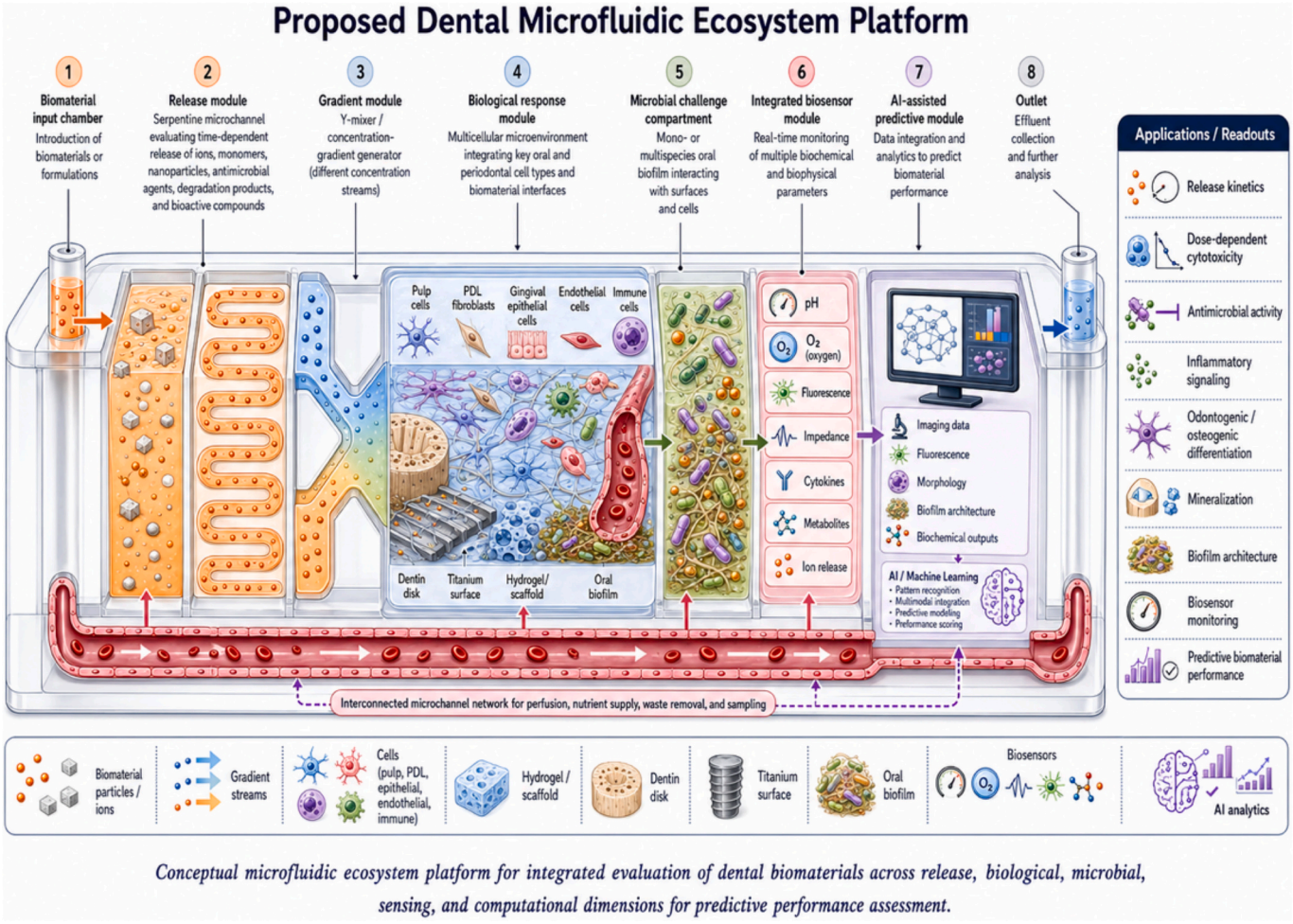


Fig. 5. Conceptual Modular Dental Microfluidic Ecosystem Platform. The schematic illustrates a future framework for integrating biomaterial release, concentration-gradient generation, biological responses, microbial challenge, biosensing, and data-assisted analysis within a modular workflow. Principal components include material input, release and gradient modules, host-cell and microbial compartments, sensors, analytical processing, and effluent collection. The figure is conceptual, not to scale, and has not been fabricated or experimentally validated. The figure was conceptually inspired by current advances in oral microphysiological systems integrating microfluidics, advanced biomaterials, nanosensors, and real-time monitoring [1,23]. All AI-related labels within the illustration denote exploratory or hypothesis-generating analytical functions and do not represent a validated capability.

and antimicrobial coating response. Finally, Fig. 6D proposes a biofilm-on-antimicrobial-biomaterial chip for assessing microbial adhesion, biofilm maturation, antimicrobial penetration, detachment under shear stress, regrowth potential, release kinetics, and antibiofilm performance. Together, these conceptual modular configurations provide a feasible stepwise pathway for validating individual functional units before progressing toward a fully integrated dental microfluidic ecosystem.

3.8. Reduction of animal models

Microfluidic OoC platforms are increasingly discussed as New Approach Methodologies (NAMs) because they can reduce, refine, and, in specific experimental contexts, partly replace animal-based testing. Their value lies in the use of human-derived cells, controlled perfusion, three-dimensional tissue architecture, biochemical gradients, and real-time analytical readouts to model biological responses that are difficult to capture in conventional assays [17]. In dental biomaterials research, this is particularly relevant for interfaces such as dentin–pulp, periodontal tissues, gingival barriers, implant surfaces, and oral biofilms [2,4,9,13].

For dental biomaterials, microfluidic platforms should currently be considered complementary NAMs rather than direct replacements for established *in vitro* or *in vivo* tests. Qualification should include comparison with applicable standards, including ISO 10993-5 for *in vitro* cytotoxicity and ISO 10993-12 for sample preparation and reference materials [43,44].

Regulatory translation requires repeatability, interlaboratory reproducibility, positive and negative controls, predefined acceptance criteria, robust fabrication, traceable materials, and concordance with established reference methods or clinically relevant outcomes.

The FDA Modernization Act 2.0 broadened the statutory framework for nonclinical testing alternatives, including cell-based assays, OoC, and computational models [17,25]. This legislative change does not itself validate any dental OoC platform. Cross-disciplinary analyses likewise emphasize context-of-use definition, technical qualification, reproducibility, and regulatory pathways [24].

3.9. Future directions

Future work in dental LoC and OoC technologies should move beyond proof-of-concept to standardized, reproducible, and clinically informative platforms. One priority is the development of personalized systems using patient-derived dental pulp stem cells, periodontal ligament fibroblasts, gingival epithelial cells, oral keratinocytes, endothelial cells, immune cells, and patient-specific microbiota. These models could

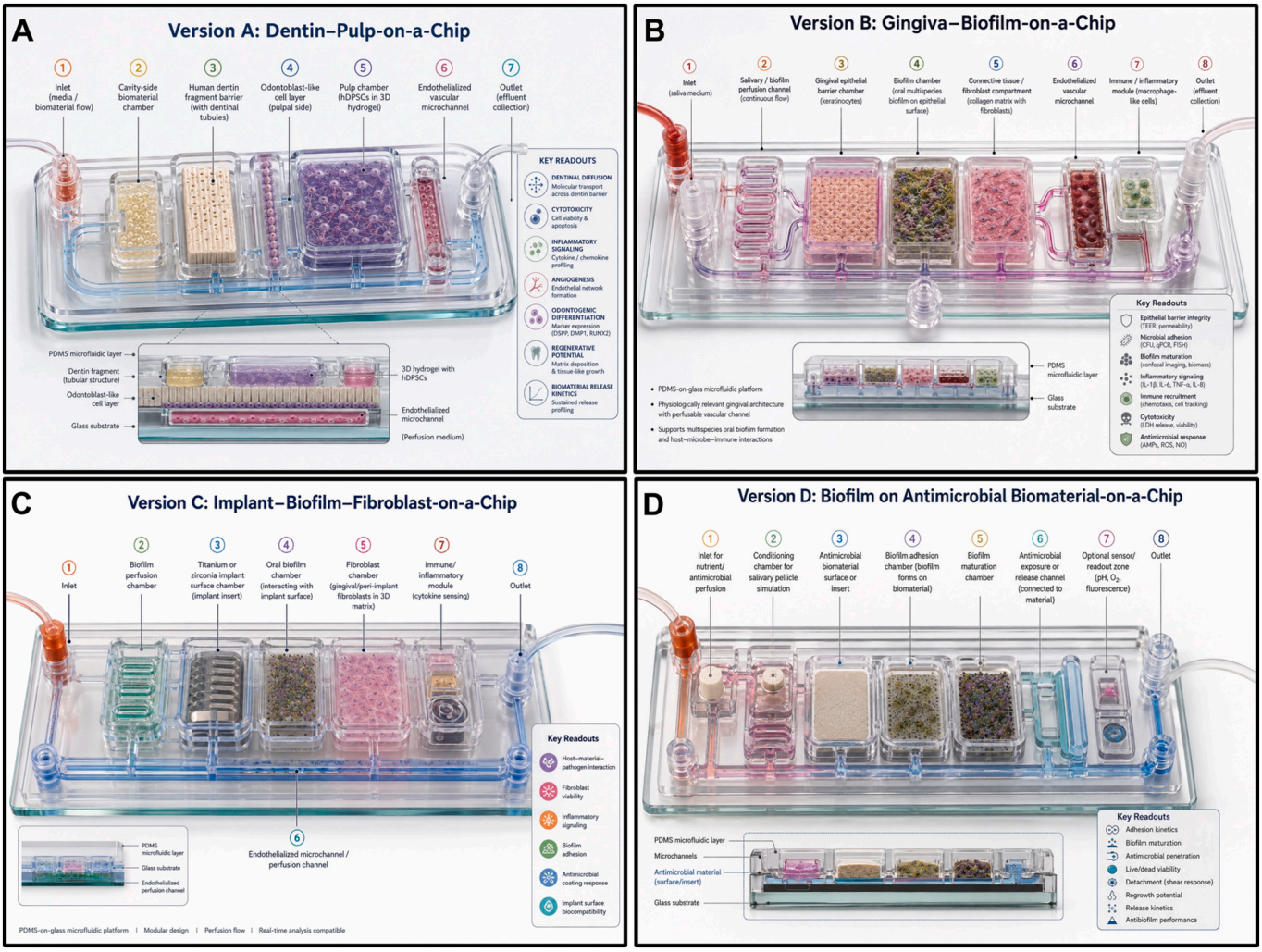


Fig. 6. Conceptual modular configurations for future dental microfluidic systems. The figure illustrates four potential configurations: (A) dentin–pulp-on-a-chip, (B) gingiva–biofilm-on-a-chip, (C) implant–biofilm–fibroblast-on-a-chip, and (D) biofilm-on-antimicrobial-biomaterial chip. These configurations depict possible functional arrangements for staged future validation. They are conceptual, not to scale, and do not represent fabricated, optimized, or experimentally validated prototypes.

support individualized biomaterial screening, regenerative endodontics, periodontal therapy, peri-implantitis research, and antimicrobial testing [1,2,10].

Greater biological complexity will also be needed. Pulpitis, periodontitis, peri-implantitis, dentin hypersensitivity, and mucosal inflammation involve immune recruitment, cytokine release, vascular remodeling, neurogenic inflammation, and sensory signaling. Incorporating macrophages, neutrophils, lymphocytes, endothelial cells, and trigeminal neuron-like components would improve the physiological relevance of dental OoC systems [11,12]. In this context, dental microfluidic models could be used not only to measure cytotoxicity or viability, but also to examine inflammation, nociceptive signaling, immune dysregulation, vascular response, and host–microbe–material interactions.

AI may become an important analytical layer in next-generation platforms. AI-assisted image analysis, cell segmentation, biofilm quantification, morphology classification, cytokine-pattern recognition, and exploratory modeling may support data-assisted interpretation of dental microfluidic outputs. These approaches may also help optimize flow rate, gradient profile, exposure time, biomaterial concentration, and scaffold composition [15,16]. Any predictive application should remain hypothesis-generating until externally validated against predefined reference standards.

Translation will depend on standardization. Future studies should report chip material, fabrication method, channel geometry, flow rate, shear stress, cell source, biomaterial preparation, biofilm conditions, exposure time, analytical endpoints, and validation strategy. Multitissue oral-on-a-chip systems integrating dentin, pulp, gingiva, periodontal ligament, vascular compartments, immune cells, neural components, biofilms, and biomaterial interfaces could provide a more faithful representation of the oral ecosystem [1,3,4]. If these requirements are addressed, dental OoC platforms may become useful tools for precision dentistry, ethical biomaterial testing, and translational oral health research.

Future research should prioritize: (1) standardized reporting of channel geometry, flow, shear stress, barrier dimensions, oxygenation, pH, and culture duration; (2) material mass-balance and adsorption studies; (3) comparison with ISO-aligned static assays; (4) inclusion of positive and negative controls; (5) assessment of intra- and interlaboratory reproducibility; (6) incorporation of clinically representative multispecies biofilms; (7) transparent cost and throughput reporting; and (8) staged validation of sensors and AI-assisted analytical pipelines.

3.10. Limitations

This review has several limitations. First, although the updated

search identified 28 eligible sources, only 21 were original experimental studies, reflecting the still limited and emerging nature of dental and oral microfluidic research. Second, the focused update was conducted using PubMed/MEDLINE, Google Scholar, citation tracking, named-model searches, and reviewer-recommended references rather than by rerunning the complete strategy in every original database. This may have introduced differential retrieval coverage. Third, original studies, dental reviews, and contextual AI or regulatory publications were required to describe the broader field, although these evidence types were analyzed separately and were not considered equivalent. Fourth, publication bias and incomplete reporting of unsuccessful or non-peer-reviewed platforms cannot be excluded. Fifth, several studies did not report key engineering parameters, including channel dimensions, shear stress, oxygenation, material adsorption, or interlaboratory reproducibility. Finally, the proposed Dental Microfluidic Ecosystem Platform remains conceptual and has not undergone fabrication, biological validation, or comparison with standardized testing frameworks.

4. Conclusion

Lab-on-a-chip and organ-on-a-chip systems offer promising tools for evaluating dental biomaterials under dynamic conditions that are not adequately captured by conventional static assays. Current models have enabled investigation of dentinal diffusion, tissue-barrier responses, host–microbe interactions, biofilm development, material release, and inflammatory signaling. However, the available evidence remains limited and heterogeneous, and critical engineering and validation parameters are still inconsistently reported.

Accordingly, these systems should currently be regarded as complementary research and qualification tools rather than validated replacements for standardized *in vitro* or animal testing. Their translational potential will depend on reproducible fabrication, standardized fluidic and biological parameters, comparison with ISO-aligned assays, interlaboratory validation, and clearly defined contexts of use. The proposed Dental Microfluidic Ecosystem Platform should therefore be considered an evidence-informed conceptual framework whose feasibility requires stepwise experimental validation.

CRediT authorship contribution statement

Rene Garcia-Contreras: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Febe Carolina Vazquez-Vazquez:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Declaration of Generative AI and AI-assisted technologies in the writing process

DALL·E, an artificial intelligence image-generation tool developed by OpenAI, was used to assist in the creation of conceptual schematic figures. The authors reviewed and approved the final figures and take full responsibility for their content.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioadv.2026.215136.

Data availability

Data will be made available on request.

References

[1] A.H.S. Wadan, D.S.A.E. El-Gemaie, A.M. Bayoumi, M.M. Zein, M.A.E.S. Ahmed, A. M. El-Khawaga, M.A.E.S. Elsayed, A.O. El-Gendy, Organ-on-chip and nano-biomaterials: next generation of precision oral and dental healthcare research, J. Nanobiotechnol. 24 (2026) 401, https://doi.org/10.1186/s12951-026-04410-5.
[2] C. Huang, F. Sanaei, W.P.R. Verdurmen, F. Yang, W. Ji, X.F. Walboomers, The application of organs-on-a-chip in dental, oral, and craniofacial research, J. Dent. Res. 102 (2023) 364–375, https://doi.org/10.1177/00220345221145555.
[3] T.V. Pierfelice, C. Giordano, F. De Angelis, S. Di Carlo, A systematic review on organ-on-a-chip in PDMS or hydrogel in dentistry: an update of the literature, Gels 10 (2024) 102, https://doi.org/10.3390/gels10020102.
[4] G. Sriram, H. Makkar, Microfluidic organ-on-chip systems for periodontal research: advances and future directions, Front. Bioeng. Biotechnol. 12 (2025) 1490453, https://doi.org/10.3389/fbioe.2024.1490453.
[5] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) n71, https://doi.org/10.1136/bmj.n71.
[6] M.L. Rethlefsen, S. Kirtley, S. Waffenschmidt, A.P. Ayala, D. Moher, M.J. Page, J. B. Koffel, PRISMA-S Group, PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews, Syst. Rev. 10 (2021) 39, https://doi.org/10.1186/s13643-020-01542-z.
[7] A.C. Tricco, E. Lillie, W. Zarin, K.K. O'Brien, H. Colquhoun, D. Levac, D. Moher, M. D.J. Peters, T. Horsley, L. Weeks, S. Hempel, E.A. Akl, C. Chang, J. McGowan, L. Stewart, L. Hartling, A. Aldcroft, M.G. Wilson, C. Garritty, S. Lewin, C. M. Godfrey, M.T. Macdonald, E.V. Langlois, K. Soares-Weiser, J. Moriarty, T. Clifford, Ö. Tunçalp, S.E. Straus, PRISMA extension for scoping reviews: checklist and explanation, Ann. Intern. Med. 169 (2018) 467–473, https://doi.org/10.7326/M18-0850.
[8] C. Baethge, S. Goldbeck-Wood, S. Mertens, SANRA—a scale for the quality assessment of narrative review articles, Res. Integr. Peer Rev. 4 (2019) 5, https://doi.org/10.1186/s41073-019-0064-8.
[9] C.M. França, A. Tahayeri, N.S. Rodrigues, S. Ferdosian, R.M. Puppin-Rontani, J. L. Ferracane, L.E. Bertassoni, The tooth on-a-chip: a microphysiologic model system mimicking the biologic interface of the tooth with biomaterials, Lab Chip 20 (2020) 405–413, https://doi.org/10.1039/C9LC00915A.
[10] H. Zhang, L. Li, S. Wang, X.-Q. Sun, C. Luo, B. Hou, Construction of dentin-on-a-chip based on microfluidic technology and tissue engineering, J. Dent. 146 (2024) 105028, https://doi.org/10.1016/j.jdent.2024.105028.
[11] A. Cordiale, D. Stanco, R. Visone, B. Stadlinger, P. Pagella, M. Rasponi, T. A. Mitsiadis, An innovative "tooth-on-chip" microfluidic device emulating the structure and physiology of the dental pulp tissue, Adv. Healthc. Mater. 15 (2026) e02080, https://doi.org/10.1002/adhm.202502080.
[12] Q. Hu, A. Acharya, H.C. Shum, W.K. Leung, G. Pelekos, Gum-on-a-chip exploring host–microbe interactions: periodontal disease modeling and drug discovery, J. Tissue Eng. 16 (2025) 20417314251314356, https://doi.org/10.1177/20417314251314356.
[13] A. Dhall, J.Y. Tan, M.J. Oh, S. Islam, J. Kim, A. Kim, G. Hwang, A dental implant-on-a-chip for 3D modeling of host–material–pathogen interactions and therapeutic testing platforms, Lab Chip 22 (2022) 4905–4916, https://doi.org/10.1039/D2LC00774F.
[14] M. Pousti, M.P. Zarabadi, M. Abbaszadeh Amirdehi, F. Paquet-Mercier, J. Greener, Microfluidic bioanalytical flow cells for biofilm studies: a review, Anal. Chim. Acta 1171 (2021) 338659, https://doi.org/10.1016/j.aca.2021.338659.
[15] S. Deng, C. Li, J. Cao, Z. Cui, J. Du, Z. Fu, H. Yang, P. Chen, Organ-on-a-chip meets artificial intelligence in drug evaluation, Theranostics 13 (2023) 4526–4558, https://doi.org/10.7150/thno.87266.

[16] A. Gangwal, A. Lavecchia, Artificial intelligence in preclinical research: enhancing digital twins and organ-on-chip to reduce animal testing, Drug Discov. Today 30 (2025) 104360, https://doi.org/10.1016/j.drudis.2025.104360.
[17] P.-J.H. Zushin, S. Mukherjee, J.C. Wu, S.M. Wu, FDA Modernization Act 2.0: transitioning beyond animal models with human cells, organoids, and AI/ML-based approaches, J. Clin. Invest. 133 (2023) e175824, https://doi.org/10.1172/JCI175824.
[18] L. An, Y. Liu, Y. Liu, Organ-on-a-chip applications in microfluidic platforms, Micromachines 16 (2025) 201, https://doi.org/10.3390/mi16020201.
[19] S. Gerke, J. Balamut, J.K. Wagner, The FDA's plan to phase out animal testing, Trends Biotechnol. S0167-7799 (25) (2026) 00532–00533, https://doi.org/10.1016/j.tibtech.2025.12.011.
[20] T.A. Mitsiadis, P. Pagella, "Dental pulp-on-chip" microfluidic devices for emulating human dental pulp tissue physiology and pathology, J. Endod. 52 (2026) 538–547, https://doi.org/10.1016/j.joen.2025.12.008.
[21] C.M. Ardila, G.A. Jiménez-Arbeláez, A.M. Vivares-Builes, The potential clinical applications of a microfluidic lab-on-a-chip for the identification and antibiotic susceptibility testing of *Enterococcus faecalis*-associated endodontic infections: a systematic review, Dent. J. 12 (1) (2024) 5, https://doi.org/10.3390/dj12010005.
[22] J. Li, J. Chen, H. Bai, H. Wang, S. Hao, Y. Ding, B. Peng, J. Zhang, L. Li, W. Huang, An overview of organs-on-chips based on deep learning, Research 2022 (2022) 9869518, https://doi.org/10.34133/2022/9869518.
[23] J. Liu, C. Du, J. Chen, B. Tang, S. Liu, J. Tan, X. Luo, J. Zhan, J. Liu, Z. Chen, Y. Zhang, Z.A. Li, W. Huang, Y. Lei, Hydrogel microspheres empowering organ-on-a-chip systems: innovations and applications, Small 21 (2025) e2504563, https://doi.org/10.1002/smll.202504563.
[24] Y. Lei, Y. Zhang, L. Zhou, Z. Zhou, M. Rothbauer, L. Bai, J. Xu, D. Xie, A. Mobasheri, X. Zhang, D. Shi, C. Ding, J. Xu, W. Huang, S. Feng, L. Yang, Y. Lai, G. Lei, Z. Luo, C. Li, J. Su, D.J. Hunter, D. Chen, Z. Gu, L. Qin, R.S. Tuan, Z.A. Li, Organoids and organs-on-chips for accelerating R&D and clinical translation in orthopaedics: emerging opportunities and regulatory pathways, J. Orthop. Transl. 56 (2026) 101021, https://doi.org/10.1016/j.jot.2025.10.013.
[25] U.S. Congress, Consolidated Appropriations Act, 2023, Pub. L. No. 117–328, div. FF, tit. III, § 3209, 136 Stat. 4459, 5821–5822, 2022.
[26] C. Rahimi, B. Rahimi, D. Padova, S.A. Rooholghodos, D.R. Bienek, X. Luo, G. Kaufman, C.B. Raub, Oral mucosa-on-a-chip to assess layer-specific responses to bacteria and dental materials, Biomicrofluidics 12 (2018) 054106, https://doi.org/10.1063/1.5048938.
[27] L. Niu, H. Zhang, Y. Liu, Y. Wang, A. Li, R. Liu, R. Zou, Q. Yang, Microfluidic chip for odontoblasts in vitro, ACS Biomater Sci. Eng. 5 (2019) 4844–4851, https://doi.org/10.1021/acsbiomaterials.9b00743.
[28] K.L. Ly, S.A. Rooholghodos, C. Rahimi, B. Rahimi, D.R. Bienek, G. Kaufman, et al., An oral-mucosa-on-a-chip sensitively evaluates cell responses to dental monomers, Biomed. Microdevices 23 (2021) 7, https://doi.org/10.1007/s10544-021-00543-6.
[29] N.S. Rodrigues, C.M. França, A. Tahayeri, Z. Ren, V.P.A. Saboia, A.J. Smith, J. L. Ferracane, H. Koo, L.E. Bertassoni, Biomaterial and biofilm interactions with the pulp-dentin complex-on-a-chip, J. Dent. Res. 100 (2021) 1136–1143, https://doi.org/10.1177/00220345211016429.
[30] L. Jin, N. Kou, F. An, Z. Gao, T. Tian, J. Hui, et al., Analyzing human periodontal soft tissue inflammation and drug responses in vitro using epithelium-capillary interface on-a-chip, Biosensors 12 (2022) 345, https://doi.org/10.3390/bios12050345.
[31] S. Hu, G. Muniraj, A. Mishra, K. Hong, J.L.L. Hong, C.H.L. Hong, V. Rosa, G. Sriram, Characterization of silver diamine fluoride cytotoxicity using microfluidic tooth-on-a-chip and gingival equivalents, Dent. Mater. 38 (2022) 1385–1394, https://doi.org/10.1016/j.dental.2022.06.025.
[32] H. Makkar, S. Radaic, E.J. Park, C.Y. Lim, G. Sriram, Modeling crevicular fluid flow and host–oral microbiome interactions in a gingival crevice-on-chip, Adv. Healthc. Mater. 12 (2023) e2202376, https://doi.org/10.1002/adhm.202202376.
[33] A.L. Gard, R.J. Luu, R. Maloney, M.H. Cooper, B.P. Cain, H. Azizgolshani, et al., A high-throughput, 28-day, microfluidic model of gingival tissue inflammation and recovery, Commun. Biol. 6 (2023) 92, https://doi.org/10.1038/s42003-023-04434-9.
[34] G. Muniraj, R.H.S. Tan, Y. Dai, R. Wu, M. Alberti, G. Sriram, Microphysiological modeling of gingival tissues and host-material interactions using gingiva-on-chip, Adv. Healthc. Mater. 12 (2023) e2301472, https://doi.org/10.1002/adhm.202301472.
[35] A. Mishra, K. Ren, S. Atkuru, Y. Dai, F. Piccinini, P.M. Preshaw, G. Sriram, Fluid flow-induced modulation of viability and osteodifferentiation of periodontal ligament stem cell spheroids-on-chip, Biomater. Sci. 13 (2023) e2303942, https://doi.org/10.1039/D3BM01011B.
[36] S. Svanberg, E. Hirth, T.A. Mitsiadis, P.S. Dittrich, "Periodontal ligament-on-chip" as a novel tool for studies on the physiology and pathology of periodontal tissues, Adv. Healthc. Mater. 13 (2024) e2303942, https://doi.org/10.1002/adhm.202303942.
[37] F. Machla, P.K. Monou, P. Artemiou, et al., Design, additive manufacturing, and characterization of an organ-on-chip microfluidic device for oral mucosa analogue growth, J. Mech. Behav. Biomed. Mater. 163 (2025) 106877, https://doi.org/10.1016/j.jmbbm.2024.106877.
[38] S. Surrency, S. Tarrah, M.A. Thuanayan, Y. Kim, R. Patil, A. Grafton, M. Curtis, P. Lialios, G.A. Kotsakis, S. Alimperti, 3D peri-implant epi-mucosa-on-a-chip reveals alterations in epithelial barrier function mediated by host–bacteria–biomaterial interactions, ACS Biomater Sci. Eng. 11 (2025) 7134–7148, https://doi.org/10.1021/acsbiomaterials.5c01232.
[39] C. Chen, J. Hui, T. Tian, L. Jin, X. Li, B. Lin, H. Liu, Biomimetic bone-vessel interface-on-a-chip for simulating periodontal physiological and pathological microenvironment, Regen. Biomater. 12 (2025) rbaf111, https://doi.org/10.1093/rb/rbaf111.
[40] S. Svanberg, M. Hanoune, T.A. Mitsiadis, P.S. Dittrich, A microfluidic model of human dental pulp angiogenesis for preclinical drug and biomaterial testing, Mater. Today Bio 37 (2026) 102776, https://doi.org/10.1016/j.mtbio.2026.102776.
[41] L. Álamo, V.T. Stuani, L.E. Correa, C.C.S.B. de Melo, I.P.M. Soares, C. Anselmi, C.A. S. Costa, J. Hebling, D.G. Soares, Trans-dentinal cytotoxicity assessment of adhesive systems on sound and caries-affected dentin using a microphysiological artificial pulp chamber system, Dent. Mater. 42 (2026) 1430–1442, https://doi.org/10.1016/j.dental.2026.03.162.
[42] J. Zhong, X. Sha, C. Dai, Y. Zeng, M. Li, J. Lu, Integrating organoids and organ-on-a-chip in dental research, Biomaterials 330 (2026) 124065, https://doi.org/10.1016/j.biomaterials.2026.124065.
[43] International Organization for Standardization, ISO 10993-5:2009, Biological Evaluation of Medical Devices—Part 5: Tests for In Vitro Cytotoxicity, ISO, Geneva, 2009.
[44] International Organization for Standardization, ISO 10993-12:2021, Biological Evaluation of Medical Devices—Part 12: Sample Preparation and Reference Materials, ISO, Geneva, 2021.