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Review article

Accelerated senescence animal models and application in dentistry: A scoping review

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Abstract Accelerated senescence models are increasingly utilized in aging research; however, their application in dental studies remains relatively limited. This scoping review investigates the use of these models within oral research. A systematic search of PubMed and Web of Science was conducted, following PRISMA-ScR guidelines and registered with the Open Science Framework, to identify relevant in vivo studies published between January 2020 and March 2025. Eligible studies involved accelerated senescence animal models in oral health contexts. Data were extracted on animal types, induction methods, aging biomarkers (e.g., P53, P21, P16, SA-β-gal), and outcomes for narrative synthesis. From 377 screened articles, 29 met the inclusion criteria. Three primary types of models were identified: chemically induced,

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physically stress-induced, and genetically based. The majority of studies focused on periodontitis (41.4 %), followed by salivary gland dysfunction. Key aging features examined included cell cycle arrest (79.3 %), senescence-associated secretory phenotypes, oxidative stress, and lysosomal alterations. Diabetes-induced aging was employed in 37.9 % of studies, and mice were the predominant animal model used (75.9 %). The findings suggest that accelerated senescence models show promise in oral aging research, especially in periodontitis and diabetes-related conditions. Incorporating multiple biomarkers may enhance model relevance and support targeted strategies in geriatric oral care.

Introduction

Aging is a universal biological process marked by a progressive decline in physiological integrity, characterized by the accumulation of cellular damage and tissue dysfunction. This deterioration leads to impaired microcirculation, multisystem failure, and ultimately compromises overall organismal health.[1,2] As the global population continues to age, according to United Nations (UN) projections, the number of adults aged 65 and older will reach 2.2 billion by 2070, placing age-related diseases at the forefront of public health concerns.[3] Among these, oral health issues are particularly prevalent yet often underrecognized. In 2021, approximately 3.69 billion people were affected by oral diseases, with conditions like severe periodontitis and tooth loss disproportionately affecting aging populations.[4,5] Furthermore, elderly individuals frequently present with systemic conditions such as diabetes and osteoporosis, which may impair bone remodeling and delay tissue healing, thereby heightening the risk of postoperative complications in dental interventions.[6,7] Despite growing awareness of these challenges, the underlying biological mechanisms of oral aging remain poorly understood. Addressing this knowledge gap is essential for developing effective, targeted strategies to improve oral health and functional outcomes in older adults.

Animal models that replicate aging processes have become indispensable tools in preclinical research, offering valuable insights into the pathophysiology of age-related oral conditions and potential therapeutic approaches.[8–10] Broadly, an aging model could be divided into natural aging models and accelerated aging models. Traditional models typically rely on naturally aged animals, however, these models are time-consuming, costly, and subject to considerable individual variability. In contrast, the accelerated aging models are more preferred due to offering distinct advantages by replicating key aging phenotypes within a shorter timeframe and under more reproducible conditions.[11,12] Commonly used artificially induced senescence models include D-galactose (D-gal) admistration,[12] senescence-accelerated mouse/prone (SAMP) strain,[11] genetic manipulation, such as Klotho-deficient mice,[13] PolgA mutation mice,[11] lamin A (LMNA) mutation model,[14] Ercc1 Δ/- mice,[15] ZMPSTE24 deficiency,[16] Rps9D95N mutation mice.[17,18] Other approaches involve exposure to external stressors, including radiotherapy and chemotherapy induced,[11] thymectomy,[12] circadian rhythm disruption,[11] and air pollution exposure (Fig. 1).[19,20] These models have been widely employed in research on neurodegeneration,[21] musculoskeletal deterioration,[22] cardiovascular dysfunction,[23] and progeroid syndromes,[14,18] demonstrating strong translational potential across multiple organ systems. However, their application within oral and craniofacial research remains limited and insufficiently explored.

To date, no comprehensive reviews have systematically addressed the establishment and application of accelerated senescence models within the context of dentistry. Unlike prior research, which may address aging in dentistry broadly, this scoping review uniquely focuses on model establishment, usage characteristics, and application prospects in the context of accelerated senescence. The findings aim to inform future investigations, promote standardisation of models, and advance translational efforts in geriatric oral healthcare.

Materials and methods

Information sources and search strategy

This scoping review was registered in the Open Science Framework registries (https://osf.io/qu6vj). The methodological framework of this study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) statement. A modified PICO(T) strategy (Patient Group or Animal species, Intervention, Comparison, Outcome measure, Time) was employed to produce a target question.[24] What is the current status of accelerated senescence animal models and application in dentistry? A comprehensive literature search was independently conducted by two investigators using both Medical Subject Headings (MeSH) and free-text terms. The search was performed across PubMed and Web of Science databases, covering studies published from January 2020 to March 2025. The detailed search strategy is provided in Supplementary 1.

Eligibility criteria

The inclusion criteria were: a) studies using accelerated senescence animal models and limited to in vivo experiments

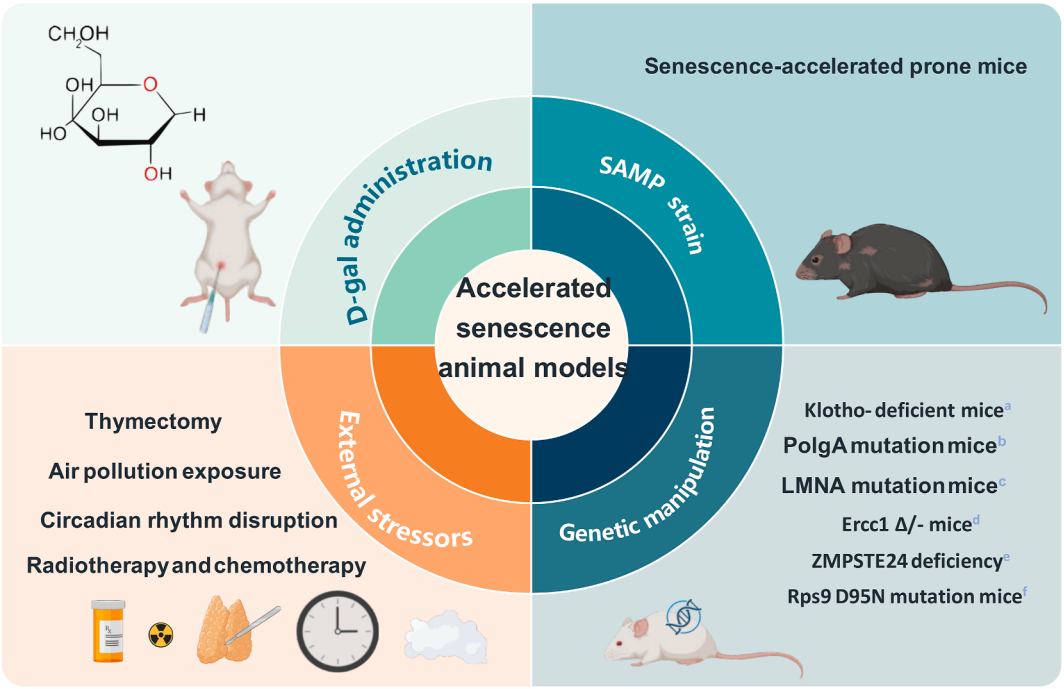

Figure 1 Overview of commonly used accelerated senescence animal models.
[a] Klotho-deficient mice: Mice deficient in the Klotho gene; [b] PolgA mutation mice: Mice with mitochondrial DNA polymerase gamma mutation; [c] LMNA mutation mice: Mice expressing mutant lamin A; [d] Ercc1 Δ/- mice: DNA repair-deficient mice; [e] ZMPSTE24 deficiency: Mice with defective lamin A processing; [f] Rps9 D95N mutation mice: Ribosomal protein mutation model (D-gal: D-galactose; SAMP: Senescence-accelerated mouse/prone).

using rodents or mammals, such as rats, mice, rabbits, dogs, pigs, and sheep, etc. b) research must involve oral-related tissues, such as periodontal tissue, alveolar bone, dental pulp, salivary glands, or oral mucosa, etc. c) interventions that induce dysfunction in oral tissues while incorporating typical aging biomarkers coherence with hallmarks of aging.[25] d) controls were naturally aging models, not treated models, animals receiving equal injections of PBS/saline and wild type (WT) control, etc. e) the key evaluation indicatorsare senescence makers:senescence-associated β-galactosidase (SA-β-gal), P16, P21, P53, senescence-associated secretory phenotype (SASP), assays involving DNA damage, telomere shortening, and cell cycle arrest.[26,27] f)the duration of the intervention is limitless, and the search covered all the literature published internationally at the time of the specified search.

The exclusion criteria were: a) in vitro experiments, observations were made on a natural model of aging, organoids, or the object of study being human. b) accelerated senescence model, but in other disciplines. c) interventions capable of inducing dysfunction in oral tissues but without typical senescence detection indicators. d) reviews and articles not published in English or without a full text were excluded.

Article selection and data extraction

The extracted data encompassed various study characteristics, including methods of inducing aging, fields of application, animal species, sex and age, treatment interventions, control or comparison groups, modes, routes and durations of induction, aging biomarkers, senescence characteristics, involvement of biomaterials, as well as author and publication year. To facilitate a clearer understanding of the current use of accelerated aging animal models and their application implications in oral science, these characteristics were systematically synthesized, organized, and narratively described. The outcomes were summarised in a manner that highlighted both the specific findings of each included study and the overarching patterns that emerged across studies. This approach allowed for a comprehensive overview of the data and offered valuable insights into current trends, research gaps, and translational potential of accelerated senescence animal models in the field of stomatology.

Results

Study selection

The initial electronic search identified 377 articles. After removing 58 duplicates, the titles and abstracts of the remaining records were screened, leading to the exclusion of 177 articles. Furthermore, one additional article was excluded due to the unavailability of the full text. A further 60 studies were excluded because they did not meet the eligibility criteria—these included studies involving naturally aged animals, in vitro experiments, human studies, or research conducted outside the relevant disciplinary scope. An additional 18 articles were excluded for lacking classical indicators of aging. Consequently, 29 articles were deemed eligible for further evaluation (Fig. 2).

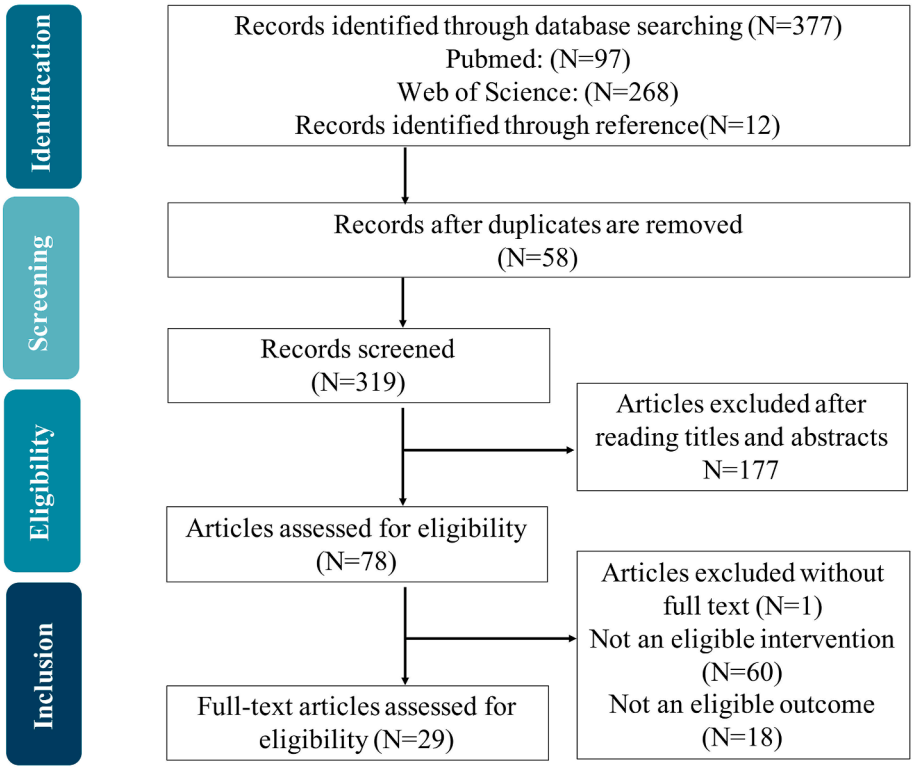

Figure 2 Search flowchart.

Study characteristics

The preliminary characteristics of these studies could be categorised into three types of senescence models: chemically induced senescence (CIS),[28–40] physical stress-induced senescence (PSIS),[41–47] and genetically based approach-induced senescence (GBAIS),[48–56] based on different driving factors.[57] Among the CIS models, D-gal-induced aging[28–32] and the streptozotocin (STZ)-injection diabetic animal model[34–39] are the most commonly used. Within the SIS, three articles employed radiation-induced cell senescence,[41–43] while the remaining four were based on exogenous stimuli.[44–47] GBAIS category can be further divided into gene-modified aging[48–52] and spontaneous genetic aging.[53–56] Moreover, the means of induction used in twenty-two studies could trigger systemic aging,[28–40,48–56] while seven studies targeted localised aging, such as specific tissues, organs.[41–47]

In terms of application, the majority of accelerated senescence models were used in studies of periodontitis (41.38 %, 12/29),[29,30,34–40,53–56] followed by salivary gland (SG) dysfunction (27.59 %, 8/29),[28,31–33,41–43,49] and orthodontic tooth movement (OTM) (6.89 %, 2/29).[44,48] Research on topics such as osteoporosis,[51] tooth and mandibular growth,[52] tooth extraction,[53] tongue carcinogenesis,[50] dental cavity preparation (DCP),[45] bone regeneration,[46] and peri-implantitis,[47] each accounted for 3.345 % (1/29) of the studies. Notably, models utilizing diabetes to induce accelerated senescence represented 37.93 % of the total studies (11/29), including seven using STZ injection,[34–40] and four involving spontaneous mutant mice.[53–56] Furthermore, the most frequently investigated senescence characteristic in all investigations was cell cycle arrest, reported in twenty-three studies (79.31 %).[28,31,34,36–54,56] This was followed by secretory phenotypes (51.72 %),[29–31,34–43,47,56] oxidative damage,[29,30,32,33,35,43,55] and lysosomal alterations (both 24.14 %).[28,42,43,46,48,50,52] Less commonly assessed were DNA damage (10.34 %),[42,43,55] mitochondrial dysfunction (6.90 %),[35,40] proliferation declined,[50] and alarmin activation (both 3.45 %).[32] In addition, 75.86 % (22/29) used mice,[28–31,34–40,42,43,48–56] 20.69 % (6/29) used rats, and 3.45 % (1/29) used mini-pigs as subjects (Fig. 3, Table 1).[41]

Accelerated senescence models and principal application in dentistry

Chemically induced senescence (CIS)model

Chemical factors, including inorganic substances, organic compounds, and functional agents such as cytotoxic drugs used in chemotherapy, have been recognized to induce cellular senescence through various pathways, such as causing irreparable DNA damage, oxidative stress, and telomerase downregulation.[58,59] Studies reviewing the in vivo adoption of animal models of accelerated senescence in dentistry have used two main instruments: D-gal-induced aging and STZ-induced aging (Fig. 4).

The D-gal-induced aging, systemic administration of D-gal has been widely used to artificially induce aging in various research fields, including studies on cardiovascular dysfunction,[23] cognitive impairment,[60] and ovarian aging.[61] At elevated concentrations, D-gal can be catalyzed by galactose oxidase into aldose and hydroperoxide, resulting in

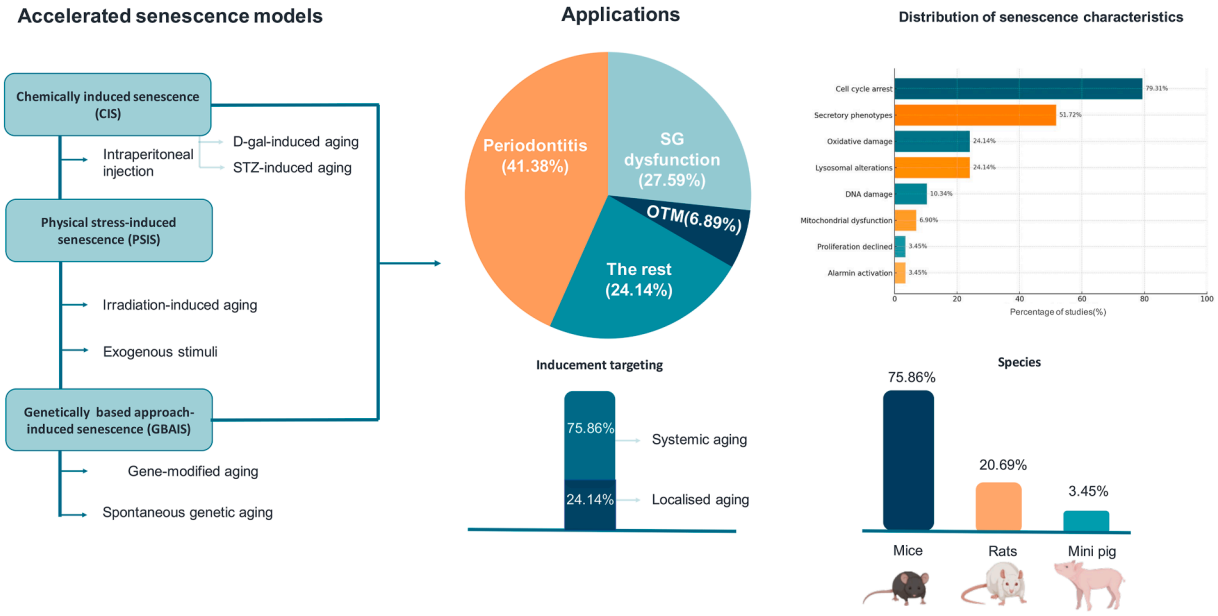

Figure 3 Schema of study characteristics.
D-gal: D-galactose; OTM: Orthodontic tooth movement; SG: Salivary gland; STZ: Streptozotocin.

the excessive generation of reactive oxygen species (ROS). This increase in ROS subsequently triggers oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis.[12] This preclinical aging model was employed in six of the studies investigated, mainly for periodontitis and SG dysfunction. In the modeling methodology, protocols involved intraperitoneal (i.p.) injections of D-gal at doses ranging from 100 to 500 mg/kg/d, with continuous administration cycles lasting from 42 days to 13 weeks. Senescence indicators used in this model have mainly focused on cell cycle arrest, secretory phenotypes and oxidative damage. Concretely, the superoxide dismutase (SOD) activity and alveolar bone loss were ameliorated in D-gal-induced aging-periodontitis used baicalin via modulating gut microbiota and metabolites, as reported by Hu et al.[29] In the model of D-gal-induced SG dysfunction, functional restoration was achieved through various interventions, including dental pulp stem cell-derived exosomes (DPSC-exos),[28] ganoderma lucidum polysaccharide (GLP),[31] gemigliptin,[32] and physical exercise.[33] These approaches improved acinar atrophy and salivary flow rate, while reducing SA-β-gal activity, inflammation and apoptosis. Interestingly, both GLP and gemigliptin were found to promote the expression of aquaporin 5 (AQP5) in two independent studies.[31,32]

The STZ-induced aging,STZ, a glucosamine-nitrosourea compound, is commonly used to induce diabetes and diabetes-related aging in animal models. STZ selectively targets pancreatic β-cells via the glucose transporter (GLUT2), causing DNA alkylation and fragmentation, leading to β-cell death and persistent hyperglycaemia.[62] Mechanistically, STZ elevates reactive ROS and advanced glycation end products (AGEs), which, in turn, activate key senescence pathways such as P53/P21Cip1 and P16Ink4a/Rb. Mitochondrial malfunction and endoplasmic reticulum (ER) stress are also prominent features, contributing to cellular energy imbalance and apoptotic signaling.[63,64] In the studies reviewed, one combined a high-fat diet (HFD) with STZ injection,[40] another utilized STZ administration along with oral P. gingivalis (P.g.) inoculation,[34] while the rest focused on STZ-induced diabetic periodontitis (DP) to explore the inflammaging.[35–39] The primary choice of injection dose varied: a small dose (50–60 mg/kg/day) administered continuously for 3–5 days or a large dose (150 mg/kg/day) given in a single session. Cell cycle arrest combined secretory phenotypes as core features are almost exclusively used in such models, and two other studies additionally assessed mitochondrial dysfunction. Metformin was used as an intervention in three studies,[36–38] and low-level laser therapy (LLLT) was used in one study,[34] both of which alleviated hyperglycaemia-induced periodontal inflammaging, as assessed by makers such as P21, P16, and SASP. Furthermore, Fu and Song separately investigated mitochondrial function in the STZ-induced inflammaging model and discovered that NIP3-like protein X (NIX) expression was decreased, alongside mitochondrial dynamic perturbations and fission.[35,40] Notably, macrophages, as key cells in the immune microenvironment, have emerged as important targets for research in this context.[34,36–38]

Physical stress-induced senescence model

Physical stimuli, referred to as mechanical stress,[65] temperature, air pollutants, ultraviolet radiation,[66] and radiotherapy,[67] can force cells to enter premature senescence by inducing increased oxidative stress and/or DNA damage, thereby activating DNA damage responses (DDR), cell cycle arrest, and the development of senescence-associated phenotypes.[68,69] Recent models of ageing research using physical means in the dental field have focused on post-operative radiotherapy and local stimulation-induced cell senescence (Fig. 4).

Irradiation-induced aging, exposure to ionizing radiation (IR) can lead to the accumulation of senescent cells, and

Table 1 Overview of the study characteristics.

Model	Induction methods	Application	Species/ Sex	Age	Treatment Intervation	Control	Method	Mode of delivery	Duration	Marker	Senescence characteristics	Biomaterial	First author (year)
Chemically induced senescence model	D-gal	SMG dysfunction	C57BL/6 mice (M)	8w	DPSC-exos	PBS	150 mg/kg/ d	i.p.	8 wk	SA-β-gal,P53, P16, P21 SASP(IL-1β,TGF-β)	Cell cycle arrest Lysosomal alterations	SMG	Zhuo Chen (2025)
	D-gal	Aging-PD	C57BL/6J mice(M)	8w	Baicalin	PBS	500 mg/kg/ d	i.p.	13wk	SOD,MDA,IL-6,TNF-α	Oxidative damage Secretory phenotypes	Alveolar bone	Huan Hu (2024)
	D-gal	Aging-PD	C57BL/6J mice (M)	8w	NA	PBS	500 mg/kg/ d	i.p.	10wk	SOD,MDA,IL-6,TNF-α	Oxidative damage Secretory phenotypes	Alveolar bone	Fangzhou Liu(2024)
	D-gal	SMG dysfunction	C57BL/6J mice (M)	8-10w	GLP	NR	120 mg/kg/ d	NR	42d	P21,P16,IL-6, TNF-α	Cell cycle arrest Secretory phenotypes	Saliva SMG	Mengna Wu(2023)
	D-gal	SG dysfunction	SD rats (M)	6w	Gemigliptin	Normal rats	300 mg/kg/ d	i.p.	4wk	ROS, HMGB1	Oxidative damage Alarmins activated	SG	Woo Kwon Jung (2024)
	D-gal	SG dysfunction	SD rats (M)	6w	Physical exercise	Young rats	100 mg/kg/ d	i.p.	6wk	ROS, 8-OHdG	Oxidative damage	SG	Woo Kwon Jung (2021)
	P.g.-STZ	DP	C57BL/6J (M)	9w	LLLT	Sodium normal saline	55 mg/kg/ d	i.p.	5d	P21,P16,SASP	Cell cycle arrest Secretory phenotypes	Periodontal tissue	Aimin Cui (2024)
	STZ	DP	C57BL/6J (M)	6-8w	NA	Vehicle	60 mg/kg/ d	i.p.	5d	MitoSOX, MDA,GSH-Px,SOD,ROS,IL-6, TNF-α,Drp1,p-Drp1, ATP level,Mfn2, COX I	Secretory phenotypes Oxidative damage Mitochondrial dysfunction	Gingiva	Xinliang Fu (2023)
	STZ	DP	C57BL/6 mice (M)	5w	Metformin	Normal saline	150 mg/kg/ d	i.p.	Single-dose	P21,P16,SASP	Cell cycle arrest Secretory phenotypes	Gingival tissue	Ziqi Yue (2023)
	STZ	DP	C57BL/6 mice (M)	18w	Metformin	CO, aged mice, yong/ aged mice + STZ	55 mg/kg/ d	i.p.	5d	P21,P16,SASP	Cell cycle arrest Secretory phenotypes	Gingival tissue	Lulingxiao Nie (2021)
	STZ	DP	C57BL/6J mice (M)	4w	Metformin	Aged mice + STZ, db/ db mice, normoglycemic	50 mg/kg/ d	i.p.	3d	P21,P16,SASP	Cell cycle arrest Secretory	Gingival tissue	Qian Wang (2021)

(*continued on next page*)

Table 1 (*continued*)

Model	Induction methods	Application	Species/ Sex	Age	Treatment Intervation	Control	Method	Mode of delivery	Duration	Marker	Senescence characteristics	Biomaterial	First author (year)
						groups, bacteria-infected db/db mice					phenotypes		
	STZ	DP	C57BL/6 mice (M)	6w	NA	Sodium	55 mg/kg/d	i.p.	5d	P21,P16,SASP	Cell cycle arrest Secretory phenotypes	Gingival tissue	Peng Zhang (2021)
	HFD + STZ	DP	C57BL/6J mice (M)	4w	NA	CO PD DM	HFD: 60 % kcal fat STZ:50 mg/kg/d	HFD: gavage STZ: i.p.	HFD: 6w STZ:5d	P21, SASP, NIX	Cell cycle arrest Secretory phenotypes Mitochondrial dysfunction	Periodontal tissue	Danni Song (2024)
Physical atress-induced senescence model	Irradiation	SG hypofunction	Miniature pigs (M)	8 mo	Transient Hedgehog activation	NT	20 Gy	IGRT	Single-dose	P53, SASP	Cell cycle arrest Secretory phenotypes	SG	Liang Hu (2021)
	Irradiation	SG hypofunction	ICR mice (F)	7-9w	hDPSC-sEV	PBS	25 Gy	IR	Single-dose	P16INK4a, $P19^{Arf}$, P21, SASP,p-H2A.X, SA-β-gal	Cell cycle arrest Secretory phenotypes Lysosomal alterations DNA damage	SMG	Jiao Dong (2021)
	Irradiation	SG hypofunction	C57BL/6 mice (NR)	NR	S1P	NT Vehicle S1P IR	15 Gy	IR	Single-dose	P53,SA-β-gal, p-H2A.X,Nox4,Sod2, Nrf2	Cell cycle arrest Secretory phenotypes Lysosomal alterations DNA damage Oxidative damage	SMG	Tao Yang (2022)
	Mechanical stress	OTM	SD rats (M)	15w	Senolytics	NT	5 N	L-loop	14d	P21,P16	Cell cycle arrest	Molar roots	Yue Zhou (2023)
	Mechanical stress	DCP	SD rats (M)	8w	Senolytics	No DCP	NA	Drilling	NA	P21,P16	Cell cycle arrest	Molar	Haitao LIU (2023)
	β-TCP granules	CSBD	SD rats(M)	8w	Senolytics	No implant	β-TCP granules	Implant	4wk	SA-β-gal,P21,P19	Cell cycle arrest Lysosomal alterations	Calvaria	Xinchen Wang (2021)
	Mini-implant + GR	Peri-implantitis	SD rats(M)	8w	Senolytics	Implant	GR	Implant	24d	P19,P21,P16, SASP	Cell cycle arrest Secretory phenotypes	Peri-implant tissue	Niuxin Yang (2023)

Genetically modified aging	Prx1-KO+ 4NQO	Tongue carcinogenesis model	C57BL/6 mice (NR)	6—8 w	NA	WT	50 μg/mL	Gavage	16 wk	P53,P21, Ki67,SA-β-gal,CDK2,CDK4, CDK6	Cell cycle arrest Cell proliferation declined Lysosomal alterations	Touge	Yunping Lu (2021)
	BDNF-KO	OTM	C57BL/6J mice (M)	8w	Exogenous BDNF	WT mice	NA	NA	NA	P16,P53,SA-β-gal	Cell cycle arrest Lysosomal alterations	Periodontal ligament	Lingxiao Meng (2023)
	Smad7-KO	SMG dysfunction	CD-1 (ICR) mice (NR)	NR	NA	WT mice	NA	NA	NA	P65	Cell cycle arrest	Saliva SMG	Minqi Hu (2021)
	Bmi 1-KO	Mandible osteoporosis	$P16^{Ink4a}{}^{+/-}$ mice (NR)	5w	AMSCs	WT mice	NA	NA	NA	P16,P21,P53,SA-β-gal	Cell cycle arrest Lysosomal alterations	Mandible	YingYin (2022)
	Bmi 1-KO	Tooth and mandible growth retardation	C57Bl/6J mice (NR)	4w	NA	WT mice, $P16^{-/-}$, $Bmi1^{-/-}$ $P16^{-/-}$	NA	NA	NA	P27,P53,CDK4	Cell cycle arrest	Mandible	YingYin (2020)
Spontaneous genetic aging	Selective breeding DM	T2DM-tooth extraction	GK rats (M)	6w	NA	Wistar rats	NA	NA	NA	P21, P16	Cell cycle arrest	Epithelial, connective tissues of extraction sockets	Chuyi LUO (2024)
	Leprdb/db mutant mice DM	DP	BKS-db/db mice (M)	4w	Metformin	BKS mice	NA	NA	NA	P21, P53	Cell cycle arrest	JE	Xiaoyuan Ye (2024)
	Leprdb/db mutant mice DM	DP	db/db mice(M)	8w	NA	WT	NA	NA	NA	TRF2,53BP1,8-OHdG,MDA, GSH-Px, SOD	DNA damage Oxidative damage	Periodontal ligament	Lu Tang (2022)
	P.g.-infected db/db mice	DP	db/db mice(M)	4w	$25(OH)D_3$	WT	NA	NA	NA	P21,P16,SASP	Cell cycle arrest Secretory phenotypes	Gingiva tissue	Qian Wang (2020)

$25(OH)D_3$: 25-Hydroxyvitamin D3; 4NQO: 4-nitro-quinoline-1-oxide; 53BP1: P53-binding protein 1; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; AMSCs: Amniotic membrane mesenchymal stem cells; BDNF: Brain-derived neurotrophic factor; BKS-db/db: C57BLKS/J-leprdb/leprdb; CDK2: Cyclin-dependent kinase 2; CDK4: Cyclin-dependent kinase 4; CDK6: Cyclin-dependent kinase 6; CO: Healthy control; COX I: Cyclooxygenase I; CSBD: Critical-sized bone defects; D-gal: D-galactose; DCP: Dental cavity preparation; DM: Diabetes mellitus; DP: Diabetic periodontitis; DPSC-exos: Dental pulp stem cell-derived exosomes; F:Female; GK: Goto-Kakizaki; GLP: Ganoderma lucidum polysaccharide; GR: Gum ring; GSH-Px: Glutathione peroxidase; HFD: High-fat diet; HMGB1: High-mobility group box 1; hDPSC-sEV: human dental pulp stem cell-derived small extracellular vesicles; ICR: Institute of cancer research; IGRT: Image-guided radiation therapy technology; IL-6: Interleukin-6; i.p.: Intraperitoneal injections; IR: Irradiation; JE: Junctional epithelium; KO: Knockdown; LLLT: Low-level laser therapy; M: Male; MDA: Malondialdehyde; MitoSOX: Red mitochondrial superoxide indicator; NA: Not applicable; NIX: NIP3-like protein; Nox4: NAPDH oxidase 4; NR: Not reported; NT: No-treated; OTM: Orthodontic tooth movement; P.g.: Porphyromonas gingivalis; PBS: Phosphate-buffered saline; PD: Periodontitis; p-Drp1: phospho-Drp1; Prx1: Peroxiredoxin1; ROS: Reactive oxygen species; SA-β-gal: Senescence-associated beta-galactosidase; SASP: Senescence-associated secretory phenotype; SD: Sprague—Dawley; SG: Salivary gland; S1P: Sphingosine-1-phosphate; SMG: Submandibular gland; SOD: Superoxide dismutase; Sod2: Superoxide dismutase 2; STZ: Streptozotocin; T2DM: Type 2 diabetes mellitus; TNF-α: Tumor necrosis factor-α; Trans: Transgenic; TRF2: Telomeric Repeat-binding Factor 2; WT: Wild type; γ-H2AX: Phosphorylated Histone H2AX; d: day; mo: months; wk: week.

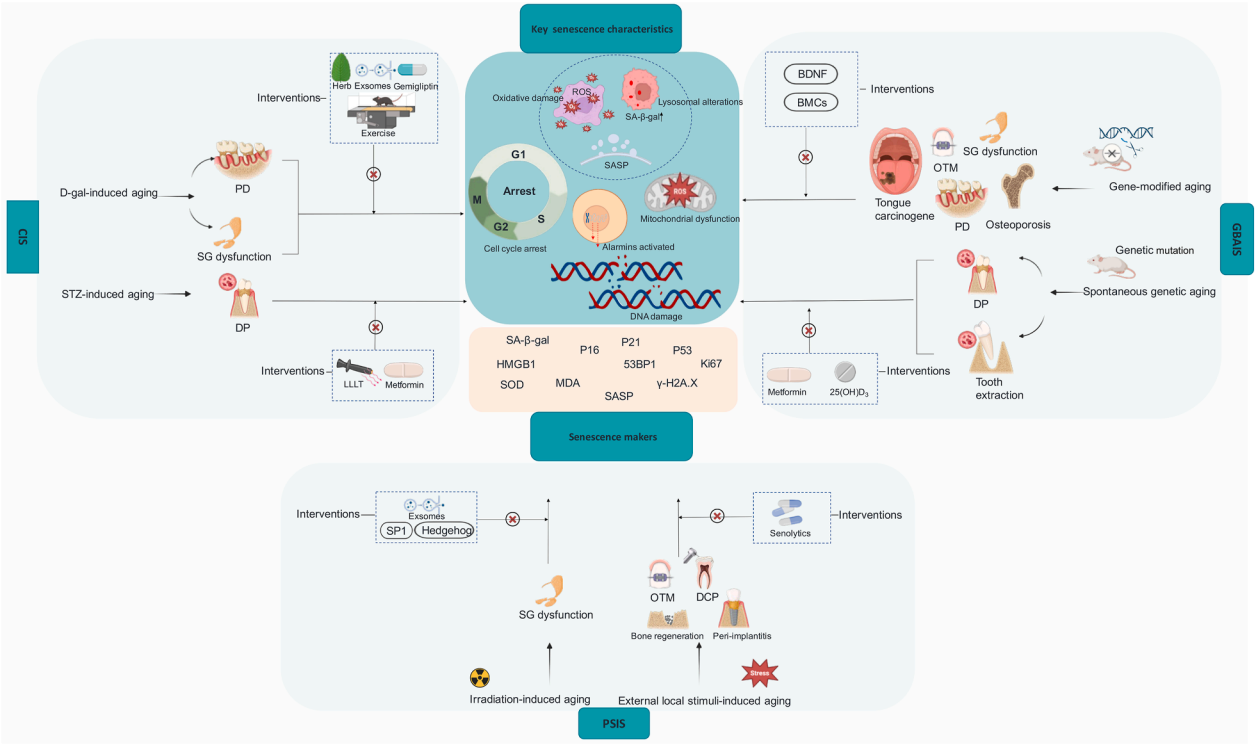

Figure 4 Accelerated senescence models and principal application in dentistry.
25(OH)D_3: 25-Hydroxyvitamin D3; BDNF: Brain-derived neurotrophic factor; CIS: Chemically induced senescence; D-gal: D-galactose; DCP: Dental cavity preparation; DP: Diabetic periodontitis; GBAIS: Genetic-based approaches induced senescence; HMGB1: High-mobility group box 1; Ki67: Proliferation marker protein Ki-67; LLLT: Low-level laser therapy; MDA: Malondialdehyde; MSCs: Membrane mesenchymal stem cells; OTM: Orthodontic tooth movement; PD: Periodontitis; PSIS: Physical stress-induced senescence; ROS: Reactive oxygen species; S1P: Sphingosine-1-phosphate; SA-β-gal: Senescence-associated beta-galactosidase; SASP: Senescence-associated secretory phenotype; SG: Salivary gland; SOD: Superoxide dismutase; STZ: Streptozotocin; γ-H2AX: Phosphorylated Histone H2AX.

this effect is dose-dependent.[70] Three studies have focused on salivary gland (SG) hypoplasia caused by radiotherapy for head and neck cancer, each establishing models of irradiation-induced senescence using species of different strain backgrounds. All three studies employed a single radiation dose between 15 and 25 Gy, targeted at the mid-neck region.[41–43] The senescence characteristics of cell cycle arrest, secretory phenotypes, lysosomal alterations and DNA damage have been observed. Hu et al. demonstrated that transient activation of Hedgehog signaling restored the functionality of irradiated SGs by promoting the recovery of resident macrophages, thereby reducing cellular senescence and inflammation.[41] Another group reported that pretreatment with sphingosine-1-phosphate (S1P) improved irradiation-induced salivary dysfunction in mice through activation of the S1pr1/Akt/eNOS pathway and decreased oxidative stress and DNA damage.[43] In addition, the use of small extracellular vesicles derived from human dental pulp stem cells (hDPSC-sEV) was identified as a promising strategy to mitigate cellular senescence, specifically in a number of phosphorylated histone H2AX (p-H2A.X) and SA-β-gal, in this model.[42]

External local stimuli-induced aging, exogenous local irritation, resulting from the specific clinical procedures performed in the oral cavity, can contribute to the development of cellular senescence with cell cycle blockade as the main feature. For example, in an orthodontic tooth movement (OTM) model involving intrusion, mechanical stress can induce senescent cells, thereby exacerbating apical root resorption.[44] Similarly, the formation of senescent cells following dental cavity preparation (DCP) may impair reparative dentin formation.[45] The implantation of beta-tricalcium phosphate (β-TCP) into bone defects has been shown to impair the function of surrounding tissues by promoting P21, P19 and SA-β-gal.[46] Additionally, a peri-implantitis model has demonstrated the induction of P21, P16 and SASP in the adjacent tissues.[47] Notably, the accumulation of these stress-induced senescent cells could be mitigated by the application of senolytic therapies.

Genetic-based approaches induced senescence (GBAIS) model

In addition to physical and chemical factors, genetic manipulation represents another primary approach for inducing accelerated aging. Generally, it can be classified into genetically modified and spontaneous genetic aging (Fig. 4).

Genetically modified aging, recent advancements in genome-editing technologies, particularly the highly efficient CRISPR/Cas system, have revolutionized genetic engineering, enabling it to be applied across a wide range of species. Models targeting key regulators such as P16Ink4a,

P21, sirtuins (SIRT family proteins), mTOR, and components of the inflammatory and DNA damage response pathways have provided insights into mechanisms of cellular senescence.[71–73] Throughout these studies that have used genetically engineered models in dentistry, cell cycle arrest and lysosomal alterations arose as key markers. The brain-derived neurotrophic factor (BDNF) heterozygous (BDNF+/−) mice strain in periodontal ligament, peroxiredoxin1 (Prx1) haploinsufficiency (Prx1+/−) in mice suppressed 4-nitro-quinoline-1-oxide (4NQO) induced tongue carcinogenesis and Smad7 knockout in mice submandibular glands (SMG) aggravated the senescence phenotype compared to wild type (WT) mice.[48,49] Furthermore, a group demonstrated that Bmi-1-deficient mice developed mandibular osteoporosis, which was associated with the upregulation of P16, P21, and P53; notably, this phenotype could be rescued by treatment with amniotic membrane-derived mesenchymal stem cells (AMSCs).[51,52]

Spontaneous genetic aging, in dentistry-related studies, spontaneous models such as Goto-Kakizaki (GK) rats and db/db mice, derived from selective breeding or natural mutation respectively, have been used to study aging-related changes in oral tissues under diabetic conditions. GK rats are a non-obese, spontaneously diabetic model derived from Wistar rats, characterized by peripheral insulin resistance, pancreatic β-cell dysfunction, and chronic inflammation, making it valuable for studying the pathophysiology and treatment of type 2 diabetes mellitus (T2DM). In contrast, db/db mice carry a spontaneous recessive mutation in the *Lepr* gene, which encodes the leptin receptor. This mutation results in defective leptin signaling, leading to severe obesity, hyperphagia, insulin resistance, and early-onset T2DM.[62,74] In these studies, the expression of cellular senescence markers such as P16Ink4a, P21, and P53, which represent cell cycle disruption, is consistently elevated in periodontal ligament,[55] gingival tissues,[56] junctional epithelium (JE),[54] or extraction sockets,[53] indicating accelerated tissue senescence. Some studies also assessed oxidative stress and DNA damage markers to further elucidate aging mechanisms.[55] Interventions such as metformin and 25-Hydroxyvitamin D3 (25(OH)D_3)supplementation have been explored for their potential to ameliorate senescence phenotypes.[54,56]

Discussion

The present scoping review provides a comprehensive overview of accelerated senescence animal models and their recent applications in dental research. Our findings reveal a growing interest in using chemically induced, physically induced, and genetically based models to simulate aging-related alterations in the oral environment. Among these, periodontitis and SG dysfunction emerged as the most frequently studied diseases.

In the research on periodontitis-related aging, two main categories of senescence models have been commonly employed. One type involves the use of D-gal induced models, which simulate systemic aging by promoting oxidative stress and cellular senescence.[29,30] The other relies on inflammation-driven aging associated with diabetic periodontitis, utilizing STZ-induced or spontaneous mutation models to replicate chronic inflammatory and metabolic conditions that accelerate periodontal degeneration.[34–40,53–56] Therapeutic strategies explored in these models, modulating gut microbiota and its metabolites may hold promise for improving senile periodontitis. Additionally, evidence indicates that systemic metformin therapy and local interventions like LLLT, both of which mitigate periodontal inflammation through senescence modulation, may offer an effective integrated avenue for managing diabetic periodontitis. In addition to the above-mentioned models that induce accelerated aging phenotypes, emerging genetic tools have enabled more precise investigations into the role of senescent cells in periodontal disease. For instance, the P16-3 MR transgenic mouse model allows selective labeling and clearance of P16Ink4a-positive senescent cells. Using this model, Chu et al. demonstrated that targeted ablation of senescent cells significantly attenuated periodontitis progression, thereby providing direct evidence for the pathogenic role of cellular senescence in periodontal tissue degeneration.[75]

Another extensively studied condition is SG dysfunction, D-gal administration and radiation-induced was modeled. Among various disease models, this condition has been associated with the most extensive application of aging hallmarks for identifying senescent cells, involving cell cyst disruption, secretory phenotypes, endogenous proteins alarmin, oxidative damage, lysosomal alterations and DNA damage. Available evidence suggests systemic or bioactive interventions may ameliorate age-related glandular hypofunction by increasing salivary flow rate and attenuating aging phenotype.[28,31–33] Approaches targeting signaling pathways, immune cell recovery, and extracellular vesicle communication have shown promise in reducing senescence, inflammation and DNA damage in radiation-induced models, which simulate SG impairment commonly observed in head and neck cancer therapy.[41–43] Furthmore, resent studies have employed organoid-based models to explore SG hypofunction caused by irradiation-induced aging.[76,77] These tissue-engineered platforms offer a novel and ethically favorable alternative for studying organ aging by recapitulating complex architecture and function in vitro, thereby reducing the need for animal use and enabling scalable mechanistic and therapeutic investigations.[78]

Meanwhile, several accelerated senescence animal models have been developed through genetic manipulation targeting bone-related regulatory pathways, offering valuable insights into age-associated skeletal changes.[48,51,52] Nonetheless, the application of these models in oral and craniofacial research remains limited. Broader, evidence-based studies across diverse senescence models are needed to validate and generalize existing findings. Notably, genetic models such as SAMP6 mice,[79] Klotho-deficient mice,[80] and ZMPSTE24-deficient mice,[81] which are well-established in systemic aging and bone metabolism research, exhibit features theoretically suitable for investigating age-related changes in dental implant osseointegration, orthodontic tooth movement, and periodontal tissue remodeling.

Furthermore, we identified emerging evidence that exogenous factors introduced during routine oral clinical procedures may trigger localized cellular senescence in surrounding tissues.[44–47] The application of senolytic

agents may rescue these senescent environments and restore regenerative potential. These findings highlight the need to consider procedure-related senescence as a previously underrecognized contributor to impaired healing or compromised therapeutic outcomes. They also point to new avenues for senescence-targeted interventions to enhance regenerative capacity and long-term success in oral treatments, particularly in aging or compromised patients.

Despite their widespread use, current aging models present notable limitations. The D-gal-induced aging model, while convenient, lacks tissue specificity, and the absence of localized periodontal assessments restricts accurate interpretation of aging-related changes in oral tissues. Conversely, accelerated aging models based on mimicking T2DM-related periodontitis may introduce confounding variables related to glucose metabolism and insulin resistance. Furthermore, although various senescence-associated phenotypes have been investigated, most commonly cell cycle arrest using a range of biomarkers tailored to specific models, many studies relied on a single biomarker, potentially resulting in biased or incomplete identification of senescent cells. In addition, valuable in situ senescence indicators,[27] including cellular senescence, such as nuclear envelope erosion, decondensation of centromeric satellite DNA, accumulation of lipid droplets, and lipid peroxidation products like 4-hydroxynonenal (4-HNE), were not addressed in the literature reviewed. Simultaneously, although various therapeutic approaches such as stem cell-derived exosomes, hyperglycemia management, and senolytic agents have been employed, the heterogeneity among models precludes definitive conclusions.

This scoping review highlights the increasing use of accelerated senescence animal models in dental research, particularly in studies focusing on periodontitis, salivary gland dysfunction, and diabetes-related oral aging. These models, induced through chemical, physical, or genetic approaches, can replicate both systemic and localized aging phenotypes. Cell cycle arrest and or secretory phenotypes were mainly senescence characteristics employed. However, the current studies reviewed only two databases published within the past five years. The analysis was challenged by considerable heterogeneity in animal species, senescence induction methods, and outcomes, alongside generally small sample sizes. This variability limits direct comparison, broader generalization, and the development of standardized protocols. Future research should prioritize the optimization and selection of appropriate models tailored to specific research objectives in dentistry, incorporating emerging hallmarks of aging and insights from aging models in other biomedical fields. Refinement and broader application of these models will be essential for advancing precision geriatric oral healthcare and for the development of targeted anti-aging interventions in dentistry.

Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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Appendix A. Supplementary data

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