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Senotherapy: scientific advances and clinical potential of senolytic therapies

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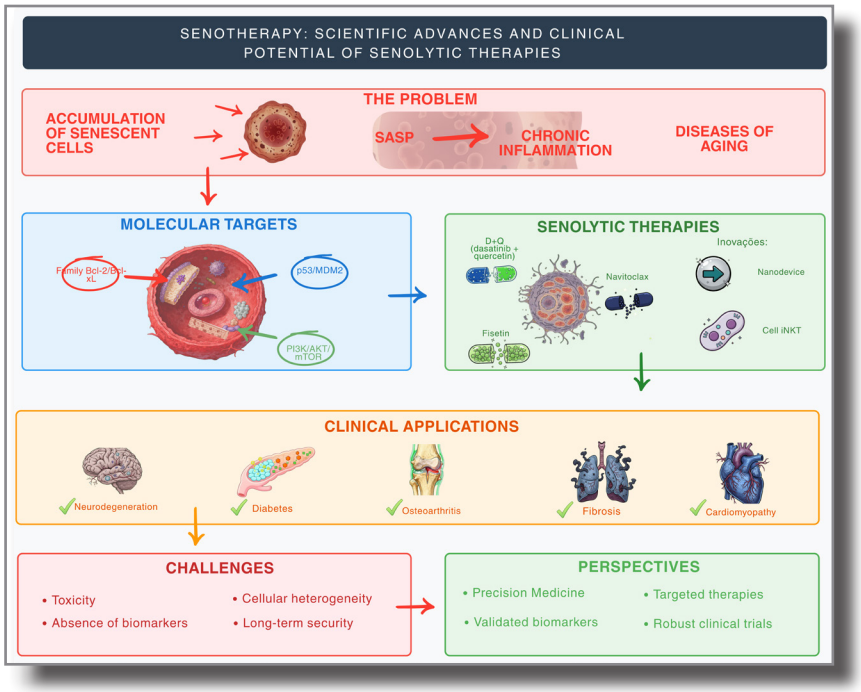
Graphical Abstract



Highlights

- *Senolytics target anti-apoptotic pathways (SCAPs), such as Bcl-2 and PI3K/AKT.*
- *Dasatinib combined with quercetin and fisetin demonstrate preclinical efficacy across multiple pathologies.*
- *Biomarkers are key to the clinical translation of senotherapy.*

Abstract

Senotherapy represents an emerging therapeutic approach to combat deleterious senescent cells, whose pro-inflammatory accumulation contributes to various aging-associated pathologies. This study aimed to analyze and systematize recent scientific advances in senotherapy, with emphasis on senolytic therapies, their innovations, and clinical potential. An integrative literature review was conducted covering the period from January 2019 to June 2025, carried out across four databases: SciELO, PubMed, ScienceDirect, and Web of Science, following PRISMA 2020 guidelines for the identification, screening, eligibility, and inclusion stages. Fifteen articles were selected from a total of 113 identified publications, with a predominance of preclinical evidence (13 of the 15 studies were restricted to *in vitro* or *in vivo* designs) and only two compounds referenced in preliminary clinical trials. The results evidence a rapidly expanding field, with a peak of scientific productivity in 2024, revealing that senolytic therapies predominantly target the modulation of anti-apoptotic pathways – such as the Bcl-2 protein family and the PI3K/AKT/mTOR pathway. Agents such as the dasatinib and quercetin combination, fisetin, and navitoclax demonstrated preclinical efficacy in models of neurodegenerative diseases, metabolic disorders, musculoskeletal and cardiovascular conditions, and in stem cell preservation. However, significant challenges persist, including on-target toxicity (e.g., navitoclax-induced thrombocytopenia), contextual heterogeneity of response across tissues and age groups, and the absence of fully validated non-invasive biomarkers in all analyzed studies for quantifying the senescent burden and monitoring therapeutic efficacy. It is concluded that senotherapy represents a promising frontier, but its clinical consolidation requires articulated advances in safety, specificity, patient stratification, and standardization, in order to translate preclinical potential into effective applications in aging medicine.

Keywords: Cellular Senescence. Senolytics. Aging. Therapeutics. Precision Medicine.

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INTRODUCTION

Population aging represents one of the main challenges for global public health in the 21st century, driving the search for interventions that not only extend longevity but also improve quality of life[1,2]. At the core of the biological mechanisms of aging and its associated diseases, cellular senescence has emerged as a fundamental process[3].

This refers to a stable cell cycle arrest in response to various stressors, in which the cell, despite ceasing its proliferation, remains metabolically active[4,5]. A central property of senescent cells is the development of a senescence-associated secretory phenotype (SASP), characterized by the release of a set of pro-inflammatory molecules, such as cytokines and chemokines. These factors alter the tissue microenvironment, potentially triggering low-grade chronic inflammation and contributing to the development of various pathologies[6,7,8].

Senescence exhibits a dualistic role: in acute contexts, it acts as a tumor suppressor mechanism and participates in tissue repair. However, the chronic accumulation of senescent cells throughout life is deleterious, being directly implicated in the pathogenesis of conditions such as neurodegenerative and cardiovascular diseases, fibrosis, and cancer[9]. This paradox established the selective elimination of senescent cells as a highly promising therapeutic strategy, giving rise to the field of senotherapy, which aims to mitigate the harmful effects of these cells[3].

Among senotherapeutic approaches, senolytics – compounds that selectively induce apoptosis in senescent cells – represent the most advanced and studied class[10]. Progress in the field has been notable, with promising preclinical results that have led to the translation of compounds such as dasatinib and quercetin into initial clinical trials, where they demonstrated potential to alleviate physical dysfunction in patients with age-related diseases[11,12].

Concurrently, the therapeutic arsenal has expanded with the development of innovative technologies aimed at improving the specificity and efficacy of senotherapy, including nanotechnology, prodrugs, and immunotherapeutic approaches such as CAR-T cells[13,2]. Despite these advances, large-scale clinical application of senolytic therapies still faces significant challenges. Issues such as potential off-target effects and associated toxicities[14], as well as the optimization of pharmacokinetics and ideal dosing regimens, remain obstacles to be overcome to ensure safety and therapeutic efficacy[15].

Beyond these translational challenges, the very speed and breadth of recent research has generated a distinct knowledge gap. Currently, findings are scattered across studies evaluating a diverse range of senolytic molecules in highly specific pathological contexts and experimental models – from diabetes in animal models to osteoarthritis in cell culture.

This specialization, while crucial for progress, hinders direct comparisons of efficacy, mechanisms of action, and safety profiles across different approaches. An integrative analysis consolidating these dispersed findings and offering a clear view of which strategies are most promising for each clinical context is therefore lacking.

It is precisely to fill this gap that the present review article proposes to analyze and systematize scientific advances in senotherapy, focusing on senolytic therapies. By mapping trends, innovations, and translational potential, we seek to address the following questions: What are the main molecular targets and clinical conditions targeted by the most studied senolytic therapies? And how do the efficacy and challenges observed in preclinical and clinical studies shape future prospects for their application in medicine?

METHODOLOGY

This is a descriptive study with a qualitative approach, of the integrative literature review type, conducted according to the six-step methodological framework proposed by Whittemore & Knafl[16] and operationalized following the systematization of Souza, Silva, and Carvalho[17]: (i) formulation of the guiding question; (ii) literature search and sampling; (iii) data collection; (iv) critical appraisal of included studies; (v) discussion of results; and (vi) presentation of the integrative synthesis. The items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)[18] relating exclusively to the identification, screening, eligibility, and inclusion stages were additionally and adaptedly adopted, for the purpose of transparency in reporting the selection process. The research protocol was previously developed by the reviewer team, containing the guiding question, eligibility criteria, databases consulted, and search strategy.

The research question was initially defined based on the specification of components following the PICOT strategy, as shown in Table 1[19,20,21]. Accordingly, the guiding question for conducting the present integrative review was: "What are the main scientific advances in senotherapy, with a focus on senolytic therapies developed in recent years, and what are their potential clinical benefits?"

Table 1 - Base strategies for electronic study search.

	PICOT Strategy
P (Population/Problem)	senescent cells / cellular senescence
I (Intervention)	senotherapy / senolytic therapies
C (Comparison)	Not applicable (review of advances)
O (Outcomes/Results)	scientific advances, clinical applications, therapeutic benefits
T (Type of study)	preclinical studies, clinical trials
Search strategy in databases	
English	("cellular senescence" OR "senescent cells" OR "senescence") AND ("senolytic therapy" OR "senolytic" OR "senolytics") AND ("evaluation research") AND ("scientific advances" OR "clinical application" OR "therapeutic benefit")

The search terms used for electronic study search on the topic were predefined based on the PICOT strategy and verified in MeSH (Medical Subject Headings – www.ncbi.nlm.nih.gov/mesh/) and DeCS (Health Sciences Descriptors – https://decs.bvsalud.org/), with the base search strategy constructed in English (Chart 1), where the terms were combined using the "AND" and "OR" operators for use within the different electronic databases.

The study adopted a temporal scope from January 2019 to June 2025, with the bibliographic survey conducted between July and September 2025 in the following scientific literature databases: Scientific Electronic Library Online (SciELO), National Library of Medicine (PubMed), ScienceDirect, and Web of Science. The base search strategy, grounded in descriptors verified in MeSH and DeCS, was adapted to the specific operational syntax of each consulted database (Table 2), preserving the conceptual structure anchored in the PICOT strategy. Filters for temporal scope, language (English), and publication type (complete original articles) were applied jointly in all databases.

Table 2 - Search strategies applied to each consulted electronic database.

	Search strategy per electronic
Database	**Applied search string**
PubMed	("cellular senescence" OR "senescent cells" OR senescence) AND ("senolytic" OR senolytics OR "senolytic therapy") AND ("evaluation research" OR "scientific advances" OR "clinical application" OR "therapeutic benefit")
Web of Science	("cellular senescence" OR "senescent cells" OR senescence) AND ("senolytic*" OR "senolytic therapy") AND ("evaluation research" OR "scientific advance*" OR "clinical application" OR "therapeutic benefit")
ScienceDirect	("cellular senescence" OR "senescent cells") AND ("senolytic" OR "senolytic therapy") AND ("clinical application" OR "therapeutic benefit")
SciELO	("cellular senescence" OR "senescence") AND ("senolytic" OR "senolytic therapy")

The article inclusion criteria were: studies addressing senescent cells/cellular senescence related to aging diseases or other pathologies; development of senolytic therapies as scientific advances, clinical applications, and related to therapeutic benefits; preclinical studies (*in vitro*, *in vivo*) and phase I–III clinical trials; and complete articles in English. In turn, excluded were: research on aging without focus on cellular senescence and with approaches to non-senolytic therapies (e.g., antioxidants); literature reviews, expert opinions, theoretical studies, studies without control groups (clinical trials), those replicated across multiple databases, and articles with incomplete or irrelevant data for the PICOT question.

The study selection process followed two stages. First, team members performed independent pre-selection, reading titles and abstracts and applying the established inclusion and exclusion criteria using the Rayyan® review manager. In the second

stage, the full texts of pre-selected articles were retrieved for complete reading to confirm eligibility. After reading all articles in full, each reference was discussed in detail to reach consensus.

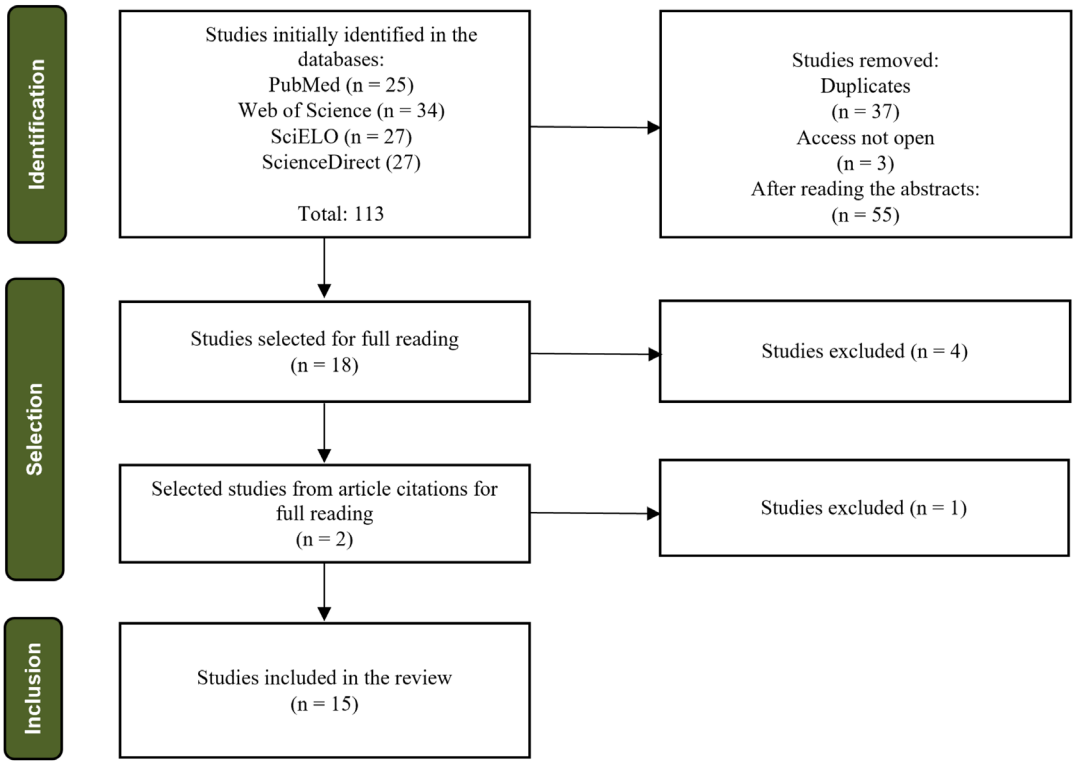
Data extraction from full texts was performed using a standardized collection instrument containing the following information: scientific journal; authors; year of publication; study location and period; objective; study design; pathology/target evaluated; senolytic drugs tested; main results and conclusions.

Critical appraisal of included studies followed the fourth stage of the integrative framework of Whittemore & Knafl[16], conducted independently by three reviewers and grounded in previously agreed qualitative criteria, namely: (i) clarity and relevance of study objectives; (ii) adequacy of the methodological design to the research question; (iii) reproducible description of experimental methods and models used; (iv) consistency between the data presented and the conclusions formulated; and (v) explicit statement of limitations by the original authors. Since this is an integrative review whose declared scope is the qualitative synthesis of the state of the art – and not the grading of evidence strength – no formal instruments for risk of bias assessment or evidence certainty hierarchization were applied. Disagreements among reviewers were resolved by consensus, with participation of a fourth reviewer when necessary.

From this instrument, data were synthesized in Microsoft Excel, version 2016, building an easily accessible and manageable database that visually displayed study results and individual syntheses, aiming to address the guiding question and, consequently, the proposed objective. The processes described were carried out by three reviewers working independently, with disagreements resolved by a fourth reviewer.

RESULTS

The database search resulted in the identification of 113 publications. After applying the inclusion and exclusion criteria, as shown in the PRISMA 2020 flowchart (Figure 1), 15 articles were selected to compose the present review.



Source: Adapted from Nazaré *et al.*[22]

Figure 1 - Selection steps according to the PRISMA 2020 flow diagram through the consulted databases.

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Chronological and geographic analysis of the selected studies reveals growing scientific interest in senotherapy, with a notable increase in publications from 2019 onward and a peak of productivity in 2024, which concentrated four of the analyzed articles. The United States emerges as the main research hub, being the country of origin of seven studies.

The academic impact of the studies is corroborated by publication in high-prestige journals, such as Nature Neuroscience and Cell Metabolism. The study by Zhang[23] presents the highest citation count (953), followed by those of Aguayo-Mazzucato[24] and Thompson[25], with 437 and 366 citations (https://www.connectedpapers.com/, as of 08/16/2025), respectively, evidencing the high repercussion of the findings within the scientific community.

Main therapeutic targets

The analyzed studies converge in identifying cell survival pathways – known as Senescent-Cell Anti-Apoptotic Pathways (SCAPs) – as the main targets of senolytic drugs. The disruption of these pathways is the predominant mechanism for the selective induction of apoptosis in senescent cells. Table 3 summarizes the main therapeutic targets and the investigated agents.

The most prominent molecular targets identified in the literature were:

• **Anti-apoptotic Pathways (SCAPs):** The Bcl-2 protein family (Bcl-2, Bcl-xL, Bcl-W) was the most recurrent target. Compounds such as navitoclax (ABT-263), venetoclax (ABT-199), and analogs demonstrated efficacy in eliminating senescent cells in models of type 1 and type 2 diabetes and oral squamous cell carcinoma[24,25,26]. Fisetin also demonstrated action, in part, through inhibition of this pathway[27,28].

Table 3 - Thematic synthesis of studies, targets, and applications of senolytic therapies. Belém, Pará, Brazil, 2025.

Thematic Category	Key Evidence	Scientific Contributions	Reference
Biological Targets of Senescence	- **Bcl-2/Bcl-xL inhibition:** navitoclax, ABT-263, ABT-199, and ABT-737 inhibit anti-apoptotic proteins, promoting selective apoptosis of senescent cells (OSCC, DM1, DM2). - **PI3K/AKT/mTOR pathway:** PF-04691502 eliminates senescent cells by inhibiting this pathway, reducing markers such as SA-β-Gal and SASP. - **Oxidative stress:** UBX0101 reduces oxidative modifications (PTMs) in post-traumatic OA, more effective in aged animals. - **SASP:** senolytics (D+Q, fisetin) reduce inflammatory cytokines, mitigating tissue dysfunction.	Identifies targets such as Bcl-2, PI3K/AKT/mTOR, oxidative stress, and SASP, elucidating survival mechanisms of senescent cells and their modulation by senolytics. Demonstrates advances in the molecular understanding of senolytic targets, with potential for targeted therapies.	24; 25; 26; 29; 30; 31; 32.
Senolytic Agents	- **D+Q:** Effective in Alzheimer's, tauopathy, COVID-19, OA, cardiomyopathy, and Crohn's disease, reducing senescence, inflammation, and cognitive deficits. - **Fisetin:** Reduces senescence in ADSCs, multiple tissues, and preserves tissue function. - **Navitoclax/ABT-263/ABT-199:** Effective in OSCC and diabetes, but with thrombocytopenia. - **UBX0101:** Reduces oxidative stress in OA. - **Nanodevices:** MMP-3-targeted navitoclax increases specificity.	Compares efficacy of D+Q (broad applicability), fisetin (potency and specificity), and BH3 mimetics (effective, but with toxicity). Highlights innovations such as nanodevices and fisetin, with trends toward safer and more specific therapies.	23; 24; 25; 26; 27; 28; 30; 33; 34; 35; 36.
Immunological Mechanisms and Surveillance	- Activation of iNKT cells eliminates senescent cells, improving glycemic control (obesity) and reducing pulmonary fibrosis.	Identifies iNKT as an immunological target for senolytics. Introduces an innovative immunotherapy-based approach, expanding senolytic strategies.	37
Stem Cell Dysfunction	- Fisetin attenuates senescence in ADSCs, preserving differentiation potential for cell therapies.	Highlights stem cell senescence as a therapeutic target. Reinforces the potential of senolytics in improving regenerative therapies as a clinical innovation.	27

Note: ABT-199: Venetoclax, selective BCL-2 inhibitor; ABT-263: Navitoclax, BCL-2 inhibitor; ABT-737: BCL-2 and BCL-xL inhibitor; ADSC: Adipose-derived mesenchymal stem cells; AKT: Protein kinase B; BCL-2: Anti-apoptotic protein; BCL-xL: Anti-apoptotic protein of the BCL-2 family; BH3: Hydrophobic groove of the BCL-2 family; D+Q: Dasatinib and Quercetin; Crohn's disease; DM1: Type 1 diabetes *mellitus*; DM2: Type 2 diabetes *mellitus*; iNKT: Invariant natural killer T cells; MMP-3: Matrix metalloproteinase-3; mTOR: Mammalian target of rapamycin; OA: Osteoarthritis; OSCC: Oral squamous cell carcinoma; PF-04691502: PI3K/mTOR inhibitor; PI3K: Phosphoinositol 3-kinase; PTM: Post-translational modifications; SASP: Senescence-associated secretory phenotype; UBX0101: Senolytic inhibitor of MDM2–p53 interaction.

• **PI3K/AKT/mTOR pathway:** inhibition of this central cell survival pathway was validated as a senolytic strategy. The compound PF-04691502, a dual PI3K/mTOR inhibitor, selectively eliminated senescent cells and suppressed the Senescence-Associated Secretory Phenotype (SASP)[29]. Quercetin and fisetin also act as inhibitors of this pathway[28,33].

• **p53/MDM2 interaction:** stabilization of p53 through inhibition of its interaction with MDM2 was another identified mechanism. The compound UBX0101 demonstrated reduced protein oxidative stress in a post-traumatic osteoarthritis model[30].

• **Matrix metalloproteinase-3 (MMP-3):** overexpression of MMP-3 by senescent cells was used as a biomarker for targeted drug delivery. A nanodevice loaded with navitoclax demonstrated selective drug release in the presence of MMP-3, increasing therapy specificity[31].

Preclinical efficacy of senolytic therapies

The selected studies provided robust evidence of senolytic efficacy across a wide range of experimental models, spanning multiple pathological categories. The main therapeutic results are summarized in Table 4.

Table 4 - Clinical potential of senolytic therapy explored in the selected studies. Belém, Pará, Brazil, 2025.

Pathological Category	Specific Condition	Senolytic Agent(s)	Primary Experimental Model	Main Therapeutic Results	Ref.
Neurodegenerative Diseases	Alzheimer's Disease (AD)	D+Q	APP/PS1 mice, human brain tissue	Reduction of OPC senescence, improvement of cognitive deficits	23
	Tauopathy	D+Q	PS19 mice	Preservation of the BBB, reduction of hyperphosphorylated tau, cognitive improvement	34
	Brain Aging / COVID-19 Neuropathology	navitoclax, ABT-737, D+Q, fisetin	Human cerebral organoids, K18-hACE2 mice	Reduction of senescence, viral load, and neuroinflammation	28
Metabolic Diseases	Type 1 Diabetes	ABT-199, ABT-737, navitoclax	NOD mice, human islets	Prevention of immune-mediated destruction of senescent beta cells	25
	Type 2 Diabetes	ABT-263, D+Q	INK-ATTAC mice	Improvement of glucose homeostasis and insulin secretion	24
Musculoskeletal Diseases	Osteoarthritis (Spontaneous)	ABT-263, D+Q	Aged mice	Reduction of pain and peripheral sensitization without alteration of tissue damage	35
	Osteoarthritis (Post-traumatic)	UBX0101	ACLT mice	Reduction of protein oxidative stress in the arthritic joint	30
Regenerative Medicine	Stem Cell Dysfunction	fisetin	Human ADSCs *in vitro*	Reduction of senescence in ADSCs, preserving differentiation potential	27
Inflammatory Diseases	Crohn's Disease	D+Q	*In vitro* model (M-SHIME, co-culture)	Modulation of microbiome dysbiosis and reduction of intestinal inflammation	33
Oncology	Oral Squamous Cell Carcinoma	4-MU + ABT-263	*OSCC* cell lines *in vitro*	Selective elimination of senescent tumor cells	26
Cardiovascular Diseases	Aging Cardiomyopathy	D+Q	Human cardiac organoids (hCOs)	Reversal of senescence markers and partial restoration of function	36
Fibrotic Diseases	Pulmonary Fibrosis	iNKT activation	Mice	Reduction of pulmonary fibrosis by elimination of senescent cells	37
Innovative Strategies	Targeted Drug Delivery	NPs(Nav)@MMP-3 nanodevice	WI-38 fibroblasts *in vitro*	Selective release of navitoclax in the presence of MMP-3	31
Age-Related Diseases (General Model)	Cell Biology / Senescence	PF-04691502	NIH-3T3 fibroblasts *in vitro*	Elimination of senescent cells with low toxicity to normal cells	29
Age-Related Diseases (General Model)	Drug Discovery	Gingerenone A	Multiple extracts *in vitro*	Identification of a novel senolytic of natural origin	32

Note: 4-MU: 4-methylumbelliferone; ACLT: Anterior cruciate ligament transection; APP/PS1: Mice expressing two mutant proteins characteristic of AD; INK-ATTAC: Express gene enabling selective elimination of p16-marked senescent cells; K18-hACE2: Mice expressing human ACE2 (receptor used by coronavirus); M-SHIME: Mucosal simulator of the human intestinal microbial ecosystem model; NIH-3T3: Fibroblast cell line derived from NIH/Swiss mouse embryos; NOD: Non-obese diabetic mice used for the study of type 1 diabetes; PS19: Mice expressing the mutant P301S form of the tau protein.

The benefits observed in preclinical models include:

• **Neurodegenerative Diseases and Brain Aging:** in models of Alzheimer's Disease and tauopathy, the dasatinib and quercetin combination (D+Q) reduced senescence of oligodendrocyte progenitor cells, decreased beta-amyloid burden and tau hyperphosphorylation, preserved blood-brain barrier integrity, and improved cognitive outcomes[23,34]. Multiple senolytics, including D+Q and fisetin, also mitigated neuroinflammation and viral burden in COVID-19 neuropathology models[28].

• **Metabolic Disorders:** in type 1 diabetes models, the elimination of senescent beta cells with Bcl-2 inhibitors prevented autoimmune destruction[25]. In type 2 diabetes models, treatment with ABT-263 or D+Q improved glucose homeostasis and insulin secretion[24].

• **Musculoskeletal Pathologies and Regenerative Medicine:** in osteoarthritis models, senolytics reduced pain hypersensitivity and protein oxidative stress[30,35]. In the field of regenerative medicine, fisetin attenuated senescence in adipose-derived mesenchymal stem cell (ADSC) cultures, preserving their differentiation potential[27].

• **Other Pathologies:** senolytic efficacy was also demonstrated in the modulation of the intestinal microbiome in a Crohn's Disease model[33], reversal of aging markers in human cardiac organoids[36], selective elimination of oral carcinoma cells[26], and reduction of pulmonary fibrosis through iNKT cell activation[37].

Comparative synthesis of pharmacological parameters

The integrated analysis of 15 studies allowed for a comparative systematization of the compounds and strategies investigated with respect to central pharmacological parameters – such as potency, specificity, toxicological profile, and stage of development – as summarized in Table 5.

Table 5 - Comparative pharmacological parameters of senolytic therapies investigated in the selected studies. Belém, Pará, Brazil, 2025.

Compound / Strategy	Molecular Target	Potency (model)	Specificity	Reported Toxicity	Stage	Reference
Navitoclax (ABT-263)	Bcl-2, Bcl-xL, Bcl-w (BH3 mimetic)	$IC_{50} \approx 0.43$ µM in WI-38 senescent cells (IR); 100 mg/kg p.o. biweekly in aged mice; 50 mg/kg/day for 4–5 days/cycle in INK-ATTAC	Selective elimination of β-Gal$^+$ cells *in vitro*; broad action on senescent cells; no change in immune cell counts	On-target thrombocytopenia and neutropenia; trabecular bone loss reported	Preclinical (*in vitro* and *in vivo*)	24; 25; 28; 31; 35
Venetoclax (ABT-199)	Selective Bcl-2	25 mg/kg p.o. on alternate days for 2 weeks in NOD mice	Selective elimination of β-senescent cells without alteration of CD4$^+$/CD8$^+$/B/macrophage counts	Reduced hematological toxicity *vs.* navitoclax (strict Bcl-2 target)	Preclinical *(in vivo)*	25
ABT-737	Bcl-2, Bcl-xL (BH3 mimetic)	100 mg/kg p.o. on alternate days for 2 weeks (NOD); 5 µM in human cerebral organoids	Selective reduction of SA-β-Gal and SASP in organoids	Expected hematological toxicity (profile analogous to navitoclax)	*In vitro* and *in vivo*	25; 28
Dasatinib + Quercetin (D+Q)	Multiple tyrosine kinases (D); HIF-1α, BCL-2, PI3K (Q)	5 mg/kg D + 50 mg/kg Q p.o. weekly in various murine models; 12 mg/kg D + 50 mg/kg Q p.o. weekly for 24 weeks (PS19); 250 nM D + 10 µM Q *in vitro*; 0.25 µM D + 10 µM Q in cardiac organoids	Broad spectrum; ~40% reduction of senescent cells *in vitro*; modulation of NF-κB, IFNγ, and IL-1α	Paradoxical cytokine modulation (IL-8 elevated in Crohn's disease); limited adverse effects in previous clinical trials	Preclinical (*in vivo*); phase I/II clinical trials ongoing	23; 24; 28; 33; 34; 35; 36
Fisetin	PI3K/AKT, BCL-2, SASP modulation (flavonoid)	50 µM (optimal dose) in ADSCs; equivalent concentration in cerebral organoids	Dose-dependent elimination; reduces 43.7% of C12FDG$^+$ cells with global viability loss of 17.5%; preserves differentiation potential in ADSCs	No significant toxicity reported in analyzed models; BBB permeability	*In vitro* and *in vivo*; preliminary clinical trials	27; 28

to be continued...

...continuation - Table 5.

Compound / Strategy	Molecular Target	Potency (model)	Specificity	Reported Toxicity	Stage	Reference
PF-04691502	PI3K/AKT/mTOR (dual inhibitor)	5 μM (optimal dose) in NIH-3T3 senescent fibroblasts; active window 5–10 μM	No effect on normal cells at 5 and 10 μM; reduction of SA-β-Gal, p16INK4a, and SASP	No relevant toxicity to non-senescent cells in the tested range	Preclinical *(in vitro)*	29
UBX0101	p53–MDM2 interaction inhibitor	1 mM in 10 μL PBS, intra-articular injection every 2 days after ACLT	Age-dependent efficacy; reduction of oxidative modifications in arthritic aged knee joint	Limited efficacy in young mice; no hematological toxicity data (local administration)	Preclinical (*in vivo*, local administration)	30
4-MU + ABT-263 (sequential combination)	Hyaluronic acid synthesis inhibitor (HAS3) + BH3 mimetic	0.5–1 mM 4-MU induces senescence in OSCC, followed by ABT-263 senolytic	Two-step strategy (senescence induction + selective senolytics); restricted to *OSCC in vitro*	4-MU: marine-derived compound considered low toxicity; ABT-263: see above	Preclinical *(in vitro)*	26
NPs(Nav)@MMP-3 Nanodevice	MMP-3-responsive release; targeted navitoclax delivery	IC_{50} senescent ≈ 0.43 μM; IC_{50} proliferating = 61.62 μM	Expanded senolytic index 5× *vs.* free navitoclax; protection of non-senescent cells	Significant attenuation of off-target toxicity of free navitoclax	Preclinical (*in vitro*, WI-38 fibroblasts)	31
Gingerenone A	Pro-apoptotic; Bcl-xL reduction; SASP modulation (natural compound)	20 μM in WI-38 senescent fibroblasts; active in 24–48 h	No effect on proliferating cells at 10 and 20 μM; reduction of IL-6 and CCL-2	No relevant toxicity in tested range	Preclinical (*in vitro)*	32
iNKT activation (α-galactosylceramide)	Immune senolytics mediated by invariant natural killer T cells	Systemic injection of α-GalCer in murine HFD and bleomycin pulmonary fibrosis models	Preferential cytotoxicity conserved in human iNKT cells	Endogenous mechanism; no systemic off-target toxicity reported	Preclinical (*in vivo*)	37

Note: Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma extra large; BH3: Bcl-2 homology 3 domain; BBB: blood-brain barrier; IC_{50}: half-maximal inhibitory concentration; HFD: high-fat diet; HIF-1α: hypoxia-inducible factor 1-alpha; iNKT: invariant natural killer T cells; IR: ionizing radiation; MMP-3: matrix metalloproteinase-3; mTOR: mammalian target of rapamycin; OSCC: oral squamous cell carcinoma; PI3K: phosphoinositol 3-kinase; SA-β-Gal: senescence-associated β-galactosidase; SASP: senescence-associated secretory phenotype; p.o.: oral administration.

The main patterns observed were:

• **Mechanistic convergence:** inhibition of anti-apoptotic SCAP pathways concentrated the majority of the investigated strategies, present in eleven of the fifteen studies, with emphasis on Bcl-2/Bcl-xL inhibitors[25,26,28,31,35], the D+Q combination[23,24,28,34,36], and fisetin[27]. Inhibition of the PI3K/AKT/mTOR pathway constituted an alternative approach documented in only one isolated compound[29]. The remaining strategies (p53/MDM2 interaction, immunosenolytics, and hyaluronic acid synthesis inhibition) were represented by individual studies[26,30,37].

• **Potency gradient:** classical BH3 mimetics demonstrated activity at nanomolar to low micromolar concentrations, with IC_{50} of 0.43 μM for navitoclax in WI-38 senescent fibroblasts[31] and effective oral doses between 25 and 100 mg/kg in murine models[24,25,35]. Natural compounds – fisetin and gingerenone A – acted at higher concentrations, on the order of 20 to 50 μM[27]. PF-04691502 showed an intermediate active window, between 5 and 10 μM[29].

• **Specificity and second-generation strategies:** second-generation compounds broadened the therapeutic window relative to non-targeted BH3 mimetics. The NPs(Nav)@MMP-3 nanodevice increased the senolytic index of navitoclax fivefold (IC_{50} proliferating/IC_{50} senescent = 61.6/0.43 μM)[31]. Activation of iNKT cells by α-galactosylceramide presented preferential cytotoxicity conserved in human cells[37]. Gingerenone A and PF-04691502 showed selectivity for senescent cells without affecting the viability of proliferating cells in the tested ranges[29].

• **Toxicological profile:** On-target toxicity related to Bcl-xL inhibition – manifesting as transient thrombocytopenia and neutropenia – was reported as a limitation of classical BH3 mimetics[31]. The D+Q combination presented paradoxical cytokine modulation in a Crohn's disease model, with elevation of IL-8 concomitant with reduction of TNF-α and CXCL-10[33]. UBX0101 demonstrated age-dependent efficacy, with superior benefit in aged mice[30].

• **Development stage: the analyzed compounds were distributed across three strata:** (i) validation restricted to *in vitro* models, represented by PF-04691502, gingerenone A, the 4-MU + ABT-263 combination, and the NPs(Nav)@MMP-3 nanodevice[26,29,31]; (ii) *in vivo* validation in murine models or human organoids, encompassing the majority of compounds[23,24,25,28,30,33,37]; and (iii) reference to

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preliminary clinical trials, recorded only for the D+Q combination and fisetin in aging-associated conditions[23,28,34]. None of the selected studies constituted a phase III clinical trial with primary clinical endpoints.

The results demonstrated that the current landscape of senolytic therapies – in terms of mechanistic scope – shows numerical predominance of strategies targeting SCAP pathways, particularly the Bcl-2 family, with the remaining target classes each represented by isolated studies. Additionally, the same compounds were applied to a diverse spectrum of clinical contexts (neurodegenerative, metabolic, articular, cardiovascular, pulmonary, oncological, and intestinal diseases), with records of site-specific responses within the same compound – exemplified by the divergent cytokine modulation by the D+Q combination in the intestinal environment[33] and by the age-dependent efficacy of UBX0101 in the articular model[30].

At the pharmacological level, concentration of studies evaluating classical BH3 mimetics (nanomolar to low micromolar range), natural compounds (concentrations on the order of 20 to 50 μM), and second-generation strategies (nanodevices, conjugates, and compounds identified through directed screening) was observed – with the latter presenting an expanded selective window in the tested models.

Additionally, the studies report wide variability in the methods used to induce cellular senescence: ionizing radiation, doxorubicin exposure, oncogenic activation, high-fat diet, and natural aging – and diversity in the primary outcomes assessed in each study. Noteworthy is the under-representation of the clinical stage in the selected set: thirteen of the fifteen studies are restricted to preclinical *in vitro* or *in vivo* designs; only two compounds – the D+Q combination and fisetin – figure with reference to preliminary clinical trials; and none of the selected studies constitutes a phase III clinical trial with primary clinical endpoints. Another characteristic identified in the research is the absence, in all 15 studies, of validated non-invasive biomarkers for quantification of senescent burden *in vivo* and for longitudinal monitoring of therapeutic response to the evaluated intervention strategies.

DISCUSSION

The results of this review consolidate the evidence that senolytic therapies constitute a therapeutic frontier with potential for treating multiple chronic diseases associated with aging. Beyond mapping recent advances in the identification of molecular targets and the validation of compounds, the integrated analysis of the 15 selected studies enables articulation of the mechanisms underlying cellular senescence and a critical positioning of the translational challenges conditioning the clinical application of this approach.

A recurring mechanistic axis in the analyzed studies is the centrality of the senescence-associated secretory phenotype (SASP) as the link between the individual senescent cell and systemic tissue dysfunction. The SASP – constituted by pro-inflammatory cytokines, chemokines, and metalloproteinases – not only perpetuates local inflammation but also influences the growth of neighboring healthy cells and induces senescence in a non-cell-autonomous manner, a phenomenon demonstrated by Thompson *et al.* through evidence of paracrine SASP transmission from senescent beta cells to intact human islets[25], and consistent with the observation by Fan *et al.* that the SASP influences neighboring cell growth and promotes chronic inflammation[29].

From this centrality arises the articulation of SASP with the immune system: failure of immunosurveillance in clearing senescent cells is identified as a driver of their tissue accumulation, and Arora *et al.* identified invariant natural killer T cells (iNKT) as an endogenous mechanism of immunosenolytics, activatable by α-galactosylceramide and dependent on recognition of CD1d overexpressed on senescent pre-adipocytes[37]. This SASP–immunity interface also manifests in the central nervous system, where Yao *et al.* demonstrated that senolytics via D+Q promote microglia transition from a disease-associated state to a homeostatic state[34], and Zhang *et al.* evidenced that removal of senescent oligodendrocyte progenitor cells reduces neuroinflammation in the beta-amyloid plaque microenvironment[23].

A second mechanistic axis emerging from the analysis is the participation of oxidative stress and mitochondrial dysfunction in the biology of senescence. Chin *et al.* position the accumulation of protein oxidative damage – produced by reactive oxygen species (ROS) derived from cellular metabolism and respiration – as a shared hallmark of biological aging, demonstrating that senolytics via UBX0101 reduce oxidative protein modification in the aged arthritic joint[30].

These findings converge with data from Scalise *et al.*, in which human cardiac organoids treated

with doxorubicin exhibited increased oxidative stress and DNA damage, reversed by the D+Q combination[36], and with those of Mullen *et al.*, who documented elevated ROS in senescent mesenchymal stem cells and their selective attenuation by fisetin[27]. Sangfuang *et al.* add the microenvironmental dimension to this articulation, describing how excess ROS arising from intestinal dysbiosis promotes chronic inflammation and facilitates the conversion of normal cells into senescent ones through activation of pathways such as NF-κB[33].

The metabolic dimension of senescence constitutes a third axis of integration. The senescent cell, despite being arrested in its proliferative cycle, remains metabolically active[24,33], and the PI3K/AKT/mTOR pathway – the central nutrient sensor and energy metabolism regulator – was validated as a senolytic target by Fan *et al.*, who identified the dual inhibitor PF-04691502 through directed screening of this pathway[29]. At the functional level, Aguayo-Mazzucato *et al.* demonstrated that senolytics – whether through the transgenic INK-ATTAC model or oral ABT-263 – improve glucose homeostasis, insulin secretion, and the genetic identity of beta cells, positioning beta-cell senescence as a determinant of type 2 diabetes progression[24]. This articulation between senescence, energy metabolism, and endocrine function illustrates that the benefit of senolytics may transcend simple cell removal, restoring functional programs of the tissue.

The analyzed studies also touch on the epigenetic remodeling accompanying senescence: Mullen *et al.* documented the formation of senescence-associated heterochromatin foci (SAHF) in mesenchymal stem cells expanded in culture, as well as their attenuation by fisetin[27] – evidence that, though singular within the analyzed set, signals chromatin reorganization as a component of the senescent phenotype.

Taken together, the articulation between SASP, oxidative stress, metabolic dysregulation, and epigenetic remodeling converges on the concept of inflammaging – explicitly invoked by Sangfuang *et al.* as a central hallmark of cellular senescence: a state of low-grade chronic inflammation fueled by the sustained secretion of pro-inflammatory mediators by metabolically active senescent cells[33]. The suppression of SASP by natural compounds, such as gingerenone A described by Moaddel *et al.*, reinforces that modulation of this secretory phenotype – and not merely the induction of apoptosis – integrates the repertoire of senotherapeutic action[32].

The D+Q combination – frequently presented as a broad-spectrum approach – presents documented limitations in the selected studies themselves. Sangfuang *et al.* reported that, in a Crohn's disease model, D+Q did not confer additional protection to intestinal barrier integrity, with non-significant changes in transepithelial electrical resistance values across all evaluated donors, and – paradoxically – induced secretion of the pro-inflammatory cytokine IL-8 in parallel with reduction of TNF-α and CXCL-10[33].

Gil *et al.*, in turn, demonstrated that D+Q combined with ABT-263 did not alter cartilage degeneration or bone changes in spontaneous osteoarthritis, being restricted to pain relief[35]. And Aguado *et al.* evidenced that individual senolytic interventions exert substantially distinct effects on the SASP – D+Q, for example, did not modulate SERPINF1 expression, unlike ABT-737[28]. Such observations indicate that the notion of "broad spectrum" must be qualified: the response to D+Q is context-dependent and, in certain tissues and outcomes, absent or paradoxical.

Another element demanding interpretive caution is the predominance of murine models in the analyzed body of evidence. The study by Chin *et al.* is particularly illustrative: senolytics via UBX0101 produced not merely distinct, but frequently opposite effects between young and aged mice, demonstrating that the tissue microenvironment of the aging organism decisively conditions the therapeutic response[30]. This age-dependency – also observed by Gil *et al.*, who reported limited chondroprotective benefit in aged mice[35] – implies that results obtained in young animals may not translate to the clinical target population, which is predominantly elderly.

Additionally, Aguayo-Mazzucato *et al.* warn of the absence of universal and consistent markers of senescence[24], and Thompson *et al.* documented that even human islets from donors with type 1 diabetes exhibit substantial variation in the expression of SASP markers – some without any marker, others with abundant expression[25] – evidencing that heterogeneity of senescence is not an artifact of animal models, but an intrinsic property of the phenomenon.

The contextual heterogeneity of the senolytic response – transversal across studies – has direct implications for clinical trial design. Tissue-specific responses, divergence between young and aged animals in the joint[30], differential modulation of SASP according to compound and tissue[28], and variation between donors in the intestinal microenvironment[33] – suggest that senotherapy will hardly benefit from universal protocols, demanding instead stratification by tissue type, age, and anti-apoptotic dependency profile of the senescent population. The success of more selective inhibitors, such as venetoclax in preventing autoimmune destruction of beta cells in type 1 diabetes[25], points

in this direction: the future of senotherapy tends toward precision, with agent selection guided by the molecular profile of the senescent cell population in each pathology.

The obstacles to clinical translation are explicitly recognized in the studies. The on-target toxicity of BH3 mimetics – notably thrombocytopenia, neutropenia, and trabecular bone loss associated with navitoclax – limits the systemic use of these compounds, and Escriche-Navarro *et al.* note that navitoclax, fisetin, and D+Q were associated with adverse effects in clinical trials[31]. This challenge drives the development of second-generation strategies: the MMP-3-responsive nanodevice developed by Escriche-Navarro *et al.* broadens the selective window by releasing navitoclax preferentially in the senescent microenvironment[31], and the immunosenolytics proposed by Arora *et al.* shift from a cytotoxic pharmacology to the restoration of endogenous immune surveillance functions[37]. Both approaches represent conceptual advances, although they remain – in the analyzed set – restricted to preclinical validation.

An additional detail revealed by the studies is the dissociation between symptomatic relief and structural repair. In osteoarthritis models, senolytics robustly relieved pain – through reduction of peripheral nociceptive signaling and axonal guidance protein expression – without reversing cartilage damage[35]. This finding indicates that, for certain conditions, the predominant clinical benefit may reside in SASP suppression and mitigation of chronic inflammation, positioning senolytics in these contexts as symptom-modifying therapy rather than structural regenerative therapy – a distinction that must be explicitly stated in the formulation of clinical expectations and outcomes.

Finally, the articulation of findings reiterates that one of the main gaps for the clinical viability of senotherapy is the absence of validated non-invasive biomarkers for quantifying the senescent burden and monitoring treatment response *in vivo* – a limitation explicitly attributed by Escriche-Navarro *et al.* to the heterogeneity of the senescent phenotype, which hinders the identification of a universal and robust marker[31]. Added to this is the fact that long-term safety and efficacy remain unknown for the majority of compounds, and that several of the analyzed studies – such as the pilot study by Sangfuang *et al.*, which explicitly acknowledges the need for longer observation periods and more robust designs[33] – explicitly signal the limits of their own inferences.

The future of senotherapy will therefore depend on the articulated overcoming of these challenges: the integration between mechanistic understanding of the crosstalk among SASP, metabolism, and immunity; the development of precision delivery strategies; and the validation of translational biomarkers constitute the conditions for converting promising preclinical findings into concrete clinical benefit for patients.

CONCLUSION

The present review consolidates senotherapy as a promising therapeutic strategy for addressing aging-associated diseases, evidencing mechanistic convergence in the inhibition of anti-apoptotic pathways (SCAPs), with predominance of Bcl-2/Bcl-xL inhibitors and the PI3K/AKT/mTOR pathway. The preclinical efficacy of agents such as the dasatinib and quercetin combination, fisetin, and navitoclax was documented in diverse models of neurodegenerative, metabolic, musculoskeletal, and cardiovascular diseases – with benefits articulated to the modulation of the senescence-associated secretory phenotype (SASP) and the crosstalk between cellular senescence, inflammaging, and immunological surveillance.

Nonetheless, effective clinical translation remains conditioned by critical challenges identified in the analyzed studies themselves: the on-target toxicity of classical BH3 mimetics (notably navitoclax-induced thrombocytopenia), the contextual heterogeneity of response across tissues and age groups, the dissociation between symptomatic relief and structural repair in certain pathologies, and the under-representation of clinical trials with robust primary endpoints in the body of evidence. It is concluded that progress in the field will depend on the articulated overcoming of three complementary fronts: the development and validation of non-invasive biomarkers for quantifying the senescent burden *in vivo* and longitudinal monitoring of therapeutic response; the stratification of patients by tissue type, age, and anti-apoptotic dependency profile of the senescent population; and the consolidation of second-generation strategies – such as senescent microenvironment-responsive nanodevices and immunosenolytic approaches – capable of enabling precision medicine in aging.

CRediT author statement

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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 paper.

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