SYSTEMATIC REVIEW

Effects of senolytic interventions on cognitive outcomes in animal models of aging and neurodegenerative disease: A systematic review

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Abstract

Background: Cellular senescence has gained increasing attention as a biological process that contributes to brain aging, neuroinflammation, and the progression of neurodegenerative disorders. The accumulation of senescent cells and their pro-inflammatory secretory profile may adversely affect neuronal function and cognitive performance. Senolytic therapies, which selectively remove senescent cells, have therefore emerged as potential interventions for age-related cognitive impairment. *Aim and Objectives:* To systematically evaluate preclinical evidence regarding the effects of senolytic interventions on cognitive outcomes in animal models of aging and neurodegenerative disease. *Methods:* A systematic review was conducted according to PRISMA 2020 recommendations. Electronic searches of PubMed and Scopus were performed up to December 31, 2025. Original in vivo studies investigating senolytic interventions and reporting cognitive or behavioural outcomes in animal models of aging or neurodegeneration were eligible for inclusion. *Results:* Seven eligible studies were included in the qualitative synthesis. The studies employed diverse rodent models, including naturally aged animals, Alzheimer's disease models, and traumatic brain injury models. Interventions evaluated included dasatinib plus quercetin, fisetin, ABT-263 (navitoclax), and genetic elimination of senescent cells. Across studies, senolytic treatment was generally associated with improved learning, memory, and other cognitive functions. Several investigations also reported reductions in neuroinflammatory markers and pathological features associated with neurodegeneration. However, methodological heterogeneity and incomplete reporting of randomization and blinding limited direct comparison among studies. *Conclusion:* Current preclinical evidence suggests that senolytic strategies may ameliorate cognitive deficits associated with aging and neurodegenerative disorders. Nevertheless, the available evidence remains limited, and additional rigorously designed animal studies are required before clinical translation can be confidently pursued.

Keywords: Cellular senescence; Senolytics; Cognitive decline; Alzheimer disease; Neurodegeneration; Animal models

Introduction

Aging is a major determinant of cognitive impairment and neurodegenerative disorders. Although increasing age is universally associated with declining physiological reserve, growing evidence suggests that specific biological processes rather than chronological aging alone contribute to progressive neural dysfunction and disease susceptibility. Among these processes, cellular senescence has emerged as an important mechanism linking aging with chronic inflammation, tissue deterioration, and functional decline across multiple organ systems [1,2].

Cellular senescence is characterized by permanent withdrawal from the cell cycle accompanied by the development of a Senescence-Associated Secretory Phenotype (SASP). Senescent cells remain

metabolically active and secrete a variety of inflammatory cytokines, chemokines, growth factors, and proteolytic enzymes that can alter tissue microenvironments and impair normal cellular function [3]. Accumulation of senescent cells has been implicated in numerous age-related pathological conditions and is increasingly recognized as a contributor to age-associated tissue dysfunction.

Within the central nervous system, senescence-related changes have been observed in several cell populations, including astrocytes, microglia, endothelial cells, oligodendrocyte progenitor cells, and, under specific circumstances, post-mitotic neurons [4,5]. The persistence of these cells may promote neuroinflammation, disrupt neuronal support functions, impair synaptic integrity, and increase vulnerability to neurodegenerative pathology [6]. Experimental studies have further demonstrated that senescent cells are not merely passive indicators of biological aging but may actively participate in disease progression and cognitive decline.

Particularly compelling evidence has emerged from studies demonstrating that selective elimination of senescent cells can attenuate neurodegenerative pathology and improve functional outcomes. Clearance of senescent glial cells has been shown to reduce tau-related pathology and preserve cognitive performance in experimental models, supporting a causal relationship between senescence and brain dysfunction [7]. These findings have strengthened interest in senescence as a potentially modifiable biological target in neurodegenerative disease.

Consequently, senolytic therapies have attracted considerable attention as a novel therapeutic approach. Senolytics are pharmacological or genetic interventions designed to selectively eliminate senescent cells while sparing healthy cells. Preclinical investigations have reported beneficial effects of senolytic therapies across several organ systems, including reductions in senescent-cell burden, attenuation of chronic inflammation, and improvement of tissue function [2,8]. In the context of brain aging, these interventions offer the possibility of targeting upstream mechanisms that contribute to cognitive decline rather than focusing exclusively on downstream pathological manifestations.

Despite increasing interest in this field, the overall quality, consistency, and translational relevance of available preclinical evidence remain uncertain. Considerable heterogeneity exists among published studies with respect to animal models, senolytic agents, treatment regimens, outcome measures, and methodological rigor. Furthermore, while cognitive outcomes are frequently reported, they are often accompanied by diverse mechanistic endpoints that complicate direct comparison across studies.

Systematic reviews of preclinical research provide an opportunity to evaluate the strength of available evidence, identify methodological limitations, and guide future translational efforts [9]. Such evaluation is particularly important in animal studies, where incomplete reporting of randomization, blinding, and allocation procedures may influence interpretation of findings and reproducibility [10]. To date, no systematic review has specifically focused on the effects of senolytic interventions on cognitive outcomes across animal models of aging and neurodegenerative disease.

Therefore, the present systematic review was undertaken to critically synthesize available preclinical evidence regarding the impact of senolytic interventions on cognitive performance in animal models of aging and neurodegeneration. By emphasizing validated behavioural outcomes and

incorporating structured assessment of methodological quality, this review aimed to clarify the consistency of reported cognitive benefits, identify important limitations within the current evidence base, and highlight priorities for future research.

Methods

Review design

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [11]. The objective was to evaluate the effects of senolytic interventions on cognitive outcomes in animal models of aging and neurodegenerative disease.

Information sources and search strategy

A structured literature search was conducted in PubMed and Scopus from database inception to December 31, 2025. Search terms were developed using combinations of controlled vocabulary and free-text keywords related to senolytic therapies, cognition, aging, neurodegeneration, and experimental animal models. Database-specific search strategies were adapted to suit indexing systems and search interfaces. Detailed search strings for each database have been provided in Supplementary File 1. To enhance retrieval of potentially relevant studies, reference lists of eligible articles were manually screened.

Eligibility criteria

Studies were eligible for inclusion if they satisfied all of the following criteria: Original peer-reviewed *in vivo* animal studies, animal models representing aging or neurodegenerative disease; administration of a senolytic intervention or genetic strategy intended to eliminate senescent cells; presence of a comparator or control group; assessment of cognitive or behavioural outcomes using validated experimental methods; publication in English.

Studies were excluded if they were *in vitro* investigations, reviews, editorials, conference abstracts, protocols, preprints without peer review, studies lacking cognitive outcome measures, or studies evaluating interventions without established senolytic activity.

Study selection

Two reviewers independently screened titles and abstracts identified through database searches. Full-text articles considered potentially relevant were subsequently assessed for eligibility. Discrepancies were resolved through discussion and consensus. Reasons for exclusion during full-text assessment were documented.

Data extraction

Data extraction was performed using a predefined standardized form. Extracted variables included animal species, strain, sex, disease model, sample size, intervention details, route of administration, treatment duration, cognitive assessment methods, comparator characteristics, and principal outcomes. Information regarding secondary mechanistic findings, including neuroinflammatory markers, neuropathological features, and indicators of senescence burden, was also collected where available.

Risk of bias assessment

Methodological quality was evaluated using the SYRCLE Risk of Bias tool for animal studies. The assessment considered sequence generation, baseline comparability, allocation concealment, random housing, blinding of outcome assessment, completeness of outcome data, selective reporting, and other potential sources of bias.

Data synthesis

A quantitative meta-analysis was not performed. Although several studies used comparable

behavioural paradigms, substantial heterogeneity was observed in animal models, disease characteristics, senolytic agents, treatment schedules, outcome definitions, and reporting methods. Consequently, calculation of pooled effect estimates was considered methodologically inappropriate. Findings were therefore synthesized narratively, with emphasis on patterns of cognitive outcomes, consistency of findings, and methodological considerations across studies.

Protocol and registration

A review protocol was developed prior to data extraction. As this review focused exclusively on preclinical animal studies, registration in PROSPERO was not applicable. Background and conceptual references were cited exclusively to contextualize senescence biology and were not considered part of the systematic synthesis unless they met predefined inclusion criteria.

Results

Study selection

A total of seven preclinical studies met the inclusion criteria and were included in the qualitative synthesis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

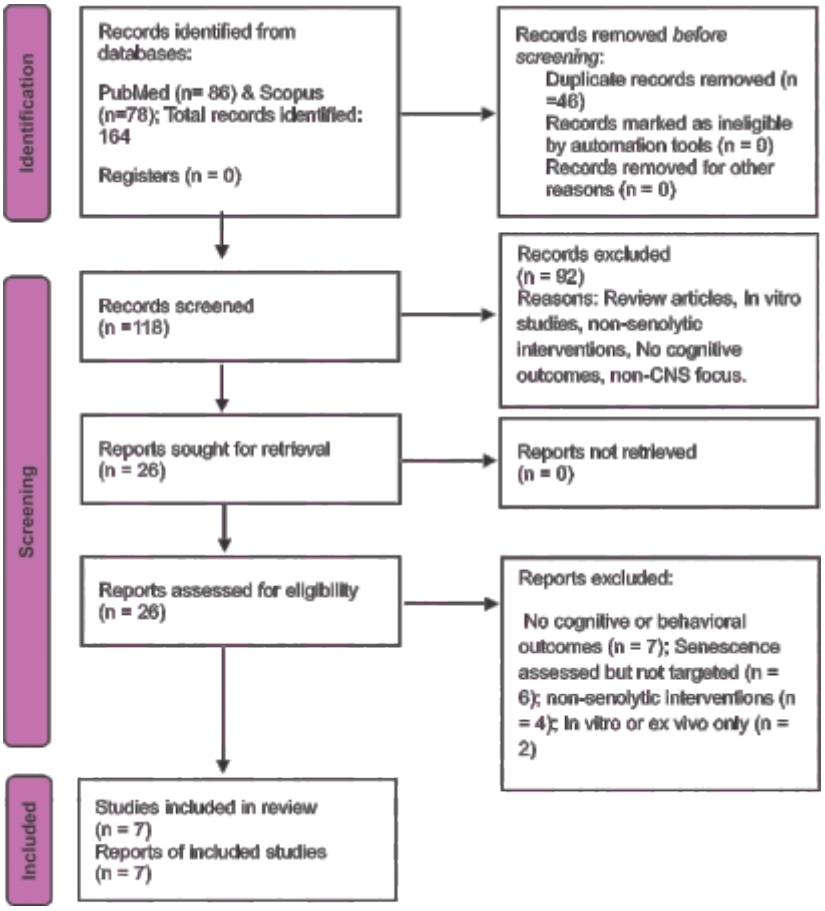

Figure 1: PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and final inclusion of 7 studies.

Study characteristics

The characteristics of the included studies are summarized in Table 1 [12-18]. All included investigations were in vivo preclinical studies conducted in rodent models of aging or neurodegenerative disease. Animal models comprised naturally aged mice, transgenic models of Alzheimer's disease, and injury-induced neurodegeneration [12-15].

Across studies, senolytic interventions included pharmacological agents and genetic approaches explicitly designed to eliminate senescent cells. Pharmacological interventions most commonly involved dasatinib combined with quercetin, fisetin, or the BCL-2 family inhibitor ABT-263. [16,18] Genetic clearance of senescent cells was employed in one study using a transgenic model enabling selective elimination of p16-Ink4a-positive cells [12].

Table 1: Characteristics of preclinical studies examining senolytic interventions and cognitive outcomes

Study (Year)	Animal model	Species / Strain	Sex	Age / Disease model	Senolytic intervention	Dosing & duration	Cognitive assessments	Key cognitive findings	Secondary outcomes
Ogrodnik *et al*. (2021) [12]	Aging	Mouse (INK-ATTAC transgenic)	Male & Female	Naturally aged (18–24 month)	Genetic clearance of p16-Ink4a+ cells	Intermittent AP20187 administration	Morris water maze, contextual fear conditioning	Clearance of senescent cells prevented age-associated memory decline	Reduced neuroinflammation; decreased senescence burden
Zhang *et al*. (2019) [13]	Alzheimer's disease	Mouse (APP/PS1)	Male	Transgenic AD model	Pharmacologic senolytic (dasatinib + quercetin)	Intermittent oral dosing	Morris water maze, Y-maze	Improved spatial learning and memory	Reduced Aβ pathology; reduced OPC senescence
Budamagunta *et al*. (2023) [14]	Aging	Mouse (C57BL/6J)	Male	Naturally aged	Pharmacologic senolytic (fisetin)	Oral administration over several weeks	Novel object recognition, Y-maze	Restoration of age-related cognitive deficits	Improved synaptic protein expression; reduced neuroinflammation
Wang *et al*. (2023) [15]	Traumatic brain injury	Mouse (C57BL/6J)	Male	Controlled cortical impact model	Pharmacologic senolytic (dasatinib + quercetin)	Post-injury intermittent dosing	Barnes maze, fear conditioning	Improved long-term memory and functional recovery	Reduced microglial activation; decreased SASP markers
Fang *et al*. (2023) [16]	Aging	Mouse (C57BL/6)	Male & Female	Middle-aged to aged	Dasatinib + quercetin or fisetin	Chronic oral administration	Morris water maze, Y-maze	Sex-dependent cognitive effects; greater benefit in males	Metabolic modulation; systemic senescence reduction
Fang *et al*. (2025) [17]	Alzheimer's disease	Mouse ($APP^{NL-F/NL-F}$)	Female	Knock-in AD model	Pharmacologic senolytic (dasatinib + quercetin)	Intermittent oral dosing	Morris water maze, novel object recognition	Improved learning and memory	Reduced amyloid pathology; metabolic improvement
Tang *et al*. (2025) [18]	Alzheimer's disease	Mouse (APP/PS1)	Male	Aged AD model	Pharmacologic senolytic (ABT-263 / navitoclax)	Repeated systemic administration	Morris water maze	Attenuation of cognitive decline	Reduced senescence markers; decreased Aβ burden

Cognitive outcomes were assessed using validated behavioural paradigms relevant to learning, memory, and executive function, including the Morris water maze, Barnes maze, Y-maze, novel object recognition, and fear conditioning tasks [13-15]. In addition to cognitive assessments, several studies reported secondary outcomes such as markers of neuroinflammation, synaptic integrity, amyloid or tau pathology, and senescence burden; however, these outcomes were not required for study inclusion.

Effects of senolytic interventions on cognitive outcomes

Across aging and neurodegenerative disease models, senolytic interventions were generally associated with improvements or preservation of cognitive performance compared with control conditions. In naturally aged animals, clearance of senescent cells prevented or attenuated age-associated impairments in spatial learning and memory [14].

In transgenic Alzheimer's disease models, senolytic interventions consistently improved spatial learning and memory outcomes. Studies employing dasatinib and quercetin, fisetin, or ABT-263 reported attenuation of cognitive decline relative to untreated transgenic controls [13,17,18]. These cognitive benefits were frequently accompanied by reductions in neuroinflammatory markers or neuropathological features, although the magnitude and consistency of these secondary effects varied across models.

In models of injury-induced neurodegeneration, senolytic treatment administered following traumatic brain injury improved long-term cognitive outcomes and functional recovery [15].

Cognitive improvements were observed across multiple behavioural paradigms and persisted beyond the acute injury phase. Sex-specific effects were examined in a limited number of studies. Where assessed, senolytic efficacy on cognitive outcomes appeared to vary by sex, with some studies reporting more pronounced benefits in one sex [16,17]. However, inconsistent reporting and limited statistical power precluded firm conclusions regarding sex-dependent effects.

Variability in animal models, senolytic agents, dosing regimens, and cognitive assays precluded meaningful quantitative pooling of outcomes.

Risk of bias assessment

The SYRCLE Risk of Bias instrument was used to evaluate the risk of bias; the results are shown in Table 2. Across studies, baseline characteristics and outcome reporting were generally well described, resulting in low risk of bias for these domains. In contrast, reporting of sequence generation, allocation concealment, random housing, and blinding procedures was frequently insufficient, leading to unclear risk of bias in several methodological domains [13,14]. No study was deemed to have a significant risk of bias due to insufficient outcome data or selective outcome reporting.

Table 2: Risk of bias assessment of included preclinical studies using the SYRCLE tool

Study (Year)	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Ogrodnik *et al*. (2021) [12]	Unclear	Low	Unclear	Unclear	Low	Low	Low
Zhang *et al*. (2019) [13]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Budamagunta *et al*. (2023) [14]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Wang *et al*. (2023) [15]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Fang *et al*. (2023) [16]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Fang *et al*. (2025) [17]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Tang *et al*. (2025) [18]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low

Discussion

This systematic review evaluated available preclinical evidence regarding the effects of senolytic interventions on cognitive outcomes in animal models of aging and neurodegenerative disease. Across the seven included studies, senolytic therapies were generally associated with preservation or improvement of cognitive performance, although the magnitude of benefit varied across experimental models and intervention strategies. Collectively, these findings support the concept that cellular senescence represents a biologically relevant and potentially modifiable contributor to cognitive decline. Nevertheless, important methodological limitations and translational uncertainties warrant careful interpretation of the current evidence.

Senescence as a therapeutic target in cognitive aging

The findings of the present review strengthen the growing hypothesis that cellular senescence contributes directly to age-related cognitive dysfunction rather than serving merely as a marker of biological aging. Senescent cells accumulate progressively with advancing age and secrete a complex mixture of inflammatory mediators, growth factors, and proteases collectively known as the SASP. Persistent exposure to these factors may disrupt neuronal homeostasis, impair synaptic plasticity, and promote neuroinflammatory processes that adversely affect cognition. In addition, senescence-related alterations in glial and vascular cells may impair neurovascular coupling and blood–brain barrier integrity, further contributing to cognitive decline [1,3,5,6].

The cognitive benefits observed following senolytic treatment across multiple studies suggest that removal of senescent cells may mitigate these detrimental effects. Importantly, beneficial outcomes were reported not only in naturally aged animals but also in models of Alzheimer's disease and traumatic brain injury, indicating that senescence-related mechanisms may contribute to cognitive impairment across diverse pathological conditions. This observation is consistent with experimental evidence demonstrating that elimination of senescent glial cells can attenuate neurodegenerative pathology and preserve cognitive function [7].

Consistency across disease models and senolytic agents

An important observation emerging from this review is the relative consistency of cognitive

improvement despite substantial variation in experimental design. Beneficial effects were reported with different senolytic approaches, including dasatinib plus quercetin, fisetin, ABT-263, and genetic clearance of p16-Ink4a-positive cells. Although these interventions act through distinct molecular pathways, they share the common objective of reducing senescent-cell burden, supporting the biological relevance of senescence clearance itself rather than drug-specific effects.

The beneficial effects observed with fisetin in the included studies are supported by previous experimental work demonstrating improvement in behavioural abnormalities and cognitive performance in animal models of Alzheimer-like pathology [19]. Although the mechanisms underlying these benefits remain incompletely understood, the convergence of findings across independent studies strengthens the rationale for further evaluation of fisetin and related senescence-targeting interventions.

The consistency of findings across aging, Alzheimer's disease, and traumatic brain injury models also suggests that senescence may represent a convergent pathological pathway underlying cognitive vulnerability. If confirmed, this would provide an attractive therapeutic target capable of influencing multiple neurodegenerative conditions through a shared upstream mechanism.

Mechanistic considerations

Although cognitive outcomes constituted the primary focus of this review, several studies also reported reductions in neuroinflammatory markers, amyloid pathology, microglial activation, and senescence-associated molecular signatures following senolytic intervention. These observations support the hypothesis that cognitive improvement may be mediated through attenuation of chronic inflammatory signalling and restoration of a more favourable neural microenvironment.

However, mechanistic conclusions should be approached cautiously. Considerable heterogeneity existed in the biomarkers assessed, and direct measurements of senescence burden were not uniformly reported across studies. Consequently, it remains difficult to determine whether cognitive improvement resulted solely from senescent-cell clearance or from additional pharmacological effects of the interventions employed.

Evidence from experimental studies has also implicated metabolic dysfunction, insulin resistance, oxidative stress, and chronic inflammation in the pathogenesis of cognitive impairment and neurodegeneration. Improvement of these upstream pathological processes has been associated with favourable cognitive outcomes in animal models, supporting the broader concept that interventions targeting fundamental biological mechanisms may offer advantages over therapies directed exclusively at downstream pathological manifestations [20].

Methodological quality and sources of heterogeneity

The present review identified several methodological concerns that limit confidence in the available evidence. Although baseline characteristics and outcome reporting were generally adequate, reporting of randomization procedures, allocation concealment, and blinding was frequently incomplete. Similar concerns have been raised previously in the preclinical literature and represent important sources of potential bias [9,10].

Substantial heterogeneity was also observed across studies. Differences were evident in animal species, disease models, intervention timing, dosing schedules, duration of treatment, and cognitive assessment methods. Such variability complicated direct comparison between studies and precluded

quantitative synthesis. Although several investigations employed commonly used behavioural paradigms such as the Morris Water Maze and Y-maze, differences in experimental protocols, outcome reporting formats, assessment time points, and statistical presentation limited the calculation of comparable effect estimates and prevented meaningful meta-analysis.

The predominance of male animals in several studies further restricts generalizability. Given emerging evidence suggesting sex-specific responses to senolytic interventions, future studies should incorporate balanced representation of both sexes and evaluate potential biological differences in treatment efficacy [16,17].

Translational implications

The translational implications of these findings are potentially significant. Unlike many therapeutic approaches that target individual downstream pathological features, senolytic interventions aim to modify a fundamental biological process implicated in aging itself. Such an approach may offer broader benefits across multiple age-related diseases, including neurodegenerative disorders.

Nevertheless, successful translation from animal models to human disease remains uncertain. Human neurodegenerative disorders develop over decades and involve complex interactions among genetic, environmental, vascular, metabolic, and immunological factors. The extent to which senescence contributes to human cognitive decline may differ substantially from that observed in experimental models. In addition, optimal treatment timing, dosing strategies, long-term safety, and target populations remain incompletely understood.

Therefore, while current findings provide encouraging proof-of-concept evidence, they should primarily be viewed as a foundation for further investigation rather than definitive support for clinical application.

Strengths and limitations of the review

The strengths of this review include adherence to PRISMA 2020 guidance, a focused research question, structured eligibility criteria, and formal assessment of methodological quality using the SYRCLE risk-of-bias tool. By concentrating specifically on cognitive outcomes, the review provides a focused synthesis of an emerging area of translational neuroscience.

Several limitations should also be acknowledged. The number of eligible studies was relatively small, methodological heterogeneity was substantial, and quantitative meta-analysis was not feasible. In addition, publication bias cannot be excluded because studies reporting positive outcomes may be more likely to be published. Restriction to English-language publications and the inclusion of only two electronic databases may also have resulted in omission of potentially relevant studies. Consequently, the magnitude of benefit associated with senolytic interventions may be overestimated.

Overall, the available evidence supports continued investigation of senescence-targeting strategies while emphasizing the need for rigorous, reproducible, and methodologically robust preclinical research before translation to clinical practice.

Conclusion

Current preclinical evidence suggests that senolytic interventions may improve cognitive outcomes in animal models of aging and neurodegenerative disease, supporting cellular senescence as a potentially modifiable contributor to cognitive decline. However, the available evidence is limited by methodological heterogeneity, incomplete reporting of key quality measures, and the small

number of eligible studies. Further well-designed preclinical investigations are required to clarify mechanisms, optimize intervention strategies, and determine the translational potential of senolytic therapies for age-related cognitive impairment.

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