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RESEARCH ARTICLE

Proteomics research in aging: a bibliometric and visualized analysis of evolution and emerging trends (1998–2024 and early 2025)

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Abstract This study aims to analyze the global research landscape and identify emerging trends in research hotspots, key technologies, and clinical applications in proteomics research in aging from 1998 to June 20, 2025. Publications related to aging and proteomics from 1998 to June 20, 2025 were retrieved from the Web of Science Core Collection. A bibliometric analysis was conducted using VOSviewer, CiteSpace, and R 4.3.3 to evaluate publication trends, research collaborations, and emerging topics. A total of 3,638 studies were included in the analysis. The USA, China, and Germany led in publication volume with 983, 829, and 227 articles respectively. Harvard University was the most prolific institution with 306 publications, followed by University of California System and Chinese Academy of Sciences. Key research was published in high-impact journals such as *Journal of Proteome Research*, *Aging Cell*, and *Proteomics*. Luigi Ferrucci, and D. Allan Butterfield were the most influential authors. Cluster analysis identified five research hotspots: protein expression and cellular senescence mechanisms, age-related diseases and neurodegeneration, cellular processes and molecular mechanisms, stress response and longevity mechanisms, and advanced proteomics technologies and biomarker discovery. Burst keyword analysis revealed recent research hotspots including health, dementia, extracellular vesicles and receptor. This study demonstrates that aging proteomics research has matured into distinct yet interconnected domains spanning basic molecular mechanisms, clinical disease applications, and technological innovations, reflecting the field's evolution toward translational and precision medicine approaches for age-related conditions. Future research directions may focus on clinical translation of aging biomarkers and development of precision medicine approaches for age-related diseases.

Keywords Aging · Proteomics · Bibliometric analysis · Research trends

Yuyuan Gao and Yinyan Xu these authors contributed equally to this work.

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Introduction

Aging is a complex biological process with profound implications for human health (Guo et al. 2022). The global population aged 65 years or older is projected to double from 771 million in 2022 to 1.6 billion by 2050, representing 16.4% of the total population (Lama 2023). This demographic shift has intensified the need to understand molecular mechanisms underlying aging, particularly protein-level changes that serve as both biomarkers and therapeutic targets (Maldonado et al. 2023; Owen et al. 2023). Proteomics, through advanced technologies such as mass spectrometry and two-dimensional gel electrophoresis, has emerged as a powerful approach for comprehensively analyzing age-related changes in protein expression, modifications, and interactions (Thikekar et al. 2023; Ubaida-Mohien et al. 2021). This methodology has provided unprecedented insights into aging mechanisms, revealing novel biomarkers for age-related diseases and potential intervention strategies (Dato et al. 2021; Ubaida-Mohien et al. 2021).

Bibliometrics represents a systematic approach to analyzing academic literature through quantitative methods, providing valuable insights into research trends, collaborative patterns, and knowledge structure within specific fields (Ninkov et al. 2022). By employing bibliometric analysis, researchers can identify crucial contributors, evaluate research impact, and track the evolution of scientific ideas over time (Passas 2024). This approach has been successfully applied across various scientific disciplines to map knowledge networks and guide future research directions (Donthu et al. 2021).

Currently, while several bibliometric studies have examined either aging or proteomics separately (Amorim et al. 2025; Wusi Zhou et al. 2025), a comprehensive analysis of the intersection between these fields is lacking. Previous reviews have focused on specific aspects of aging biology or proteomic techniques (Ascandari et al. 2023; Niu et al. 2025), but none have systematically evaluated the global research landscape of aging proteomics. Understanding the current state and trends in this field is crucial for identifying research gaps and opportunities for future investigation. While previous bibliometric studies have examined either aging or proteomics separately, this study provides the first comprehensive analysis specifically at the intersection of these two fields, using a multi-tool approach to map its unique knowledge structure, collaborative networks, and evolutionary trajectory. The present study aims to systematically assess the global research landscape and progress in aging-related proteomics research through bibliometric analysis.

Materials and methods

Search strategy

This study conducted a comprehensive literature search utilizing the Web of Science Core Collection (WoSCC) (https://www.webofscience.com/wos/woscc/basic-search) on June 20, 2025. The search strategy employed was as follows: TS = ("Aging" or "Senescence" or "ageing") AND TS = ("Proteomic*" or "Peptidomic*" or "proteome*"). The publication language was set to English, and the type of documents was set to "articles". For each identified publication, the study systematically collected data pertaining to the number of publications and citations, titles, author affiliations, institutions, countries/regions, keywords, and journal names.

Data analysis

Three robust bibliometric analysis tools were employed to thoroughly evaluate the academic landscape during the visualization process. VOSviewer (version 1.6.20) is a bibliometric analysis software that can extract key information from numerous publications (Van Eck et al. 2010), which is often used to build collaboration, co-citation, and co-occurrence networks. In our study, the software mainly completes the following analysis: country and institution analysis, journal and co-cited journal analysis, author and co-cited author analysis, and keyword co-occurrence analysis. In the map produced by VOSviewer, a node represents an item such as country, institution, journal, or author. Node size and color indicate the number and classification of these items, respectively. Line thickness between nodes reflects the degree of collaboration or co-citation of the items.

CiteSpace (version 6.3.R1) is another software developed by Professor Chen C for bibliometric analysis and visualization (Chen 2006). In our

study, CiteSpace was applied to analyze references with Citation Bursts. The R 4.3.3 was applied for thematic evolution analysis and to construct a global distribution network of publications on aging and proteomics research (Aria et al. 2017). The quartile and impact factor of the journal are obtained from Journal Citation Reports 2023.

This study employed the h-index to quantify the academic impact of individuals and journals, respectively. The h-index is a vital indication to evaluate the academic contribution of researchers and could predict their future scientific achievements (Bertoli-Barsotti et al. 2017; Hirsch 2005). In this study, h-index of each author was obtained from WoSCC. The m-index, calculated by dividing the h-index by the number of years since the author's first publication, was used to account for researchers' career length (Novak et al. 2011). The g-index, which gives more weight to highly cited articles, was calculated to complement the h-index in evaluating research impact (Ali 2021). Journal impact factors (IF) from Journal Citation Reports 2023 were used to assess journal influence in the field (Gould 2023).

Results

An overview of publications in research of aging and proteomics

A total of 3,638 publications on aging and proteomics indexed between 1 January 1998 and 20 June 2025 were identified (Fig. 1). Our investigation showed that 25,326 authors from 14,652 institutions contributed to the production of these manuscripts. These works were published in 922 journals, citing 166,654 references. The number of published articles showed an overall upward trend, with the annual publications increasing steadily over the study period (Fig. 2). The cumulative publication count reached 3,638, while annual output showed consistent growth from minimal publications in the early years (1 publication in 1998) to peaking at 407 publications in 2024. The year 2025 shows 226 publications as of June 20, 2025, representing a partial-year count.

Analysis of countries

The USA led in publication volume (983 articles), followed by China (829 articles) and Germany (227 articles). Other significant contributors included the UK (173 articles), Italy (151 articles), and Spain (130 articles). Regarding total citations (TC), the USA ranked first (47,288), while China (15,313) and Germany (9,069) followed. The UK recorded 8,161 total citations, Italy achieved 4,976 citations, and France garnered 4,331 citations. The USA also demonstrated the highest average citations per article (48.1) among major contributors, followed by the UK (47.2) and Germany (40.0) (Fig. 3A**,** Table S1). Among the 63 countries engaged in international collaborations with at least three published articles, the USA (total link strength = 966) had the highest number of partnerships, followed by Germany (total link strength = 544) and the UK (total link strength = 507) (Fig. 3B).

Analysis of the institutions

A total of 14,652 institutions contributed to research in aging proteomics, with Harvard University leading the output with 306 publications, followed by University of California System (283) and Chinese Academy of Sciences (216) (Fig. 4A). Other prominent institutions included National Institutes of Health (NIH)—USA (190), University of Texas System (189), Harvard University Medical Affiliates (179), Stanford University (172), University of Washington (165), University of Washington Seattle (165), and Centre National de la Recherche Scientifique (CNRS) (92). Among 143 institutions with at least 13 publications engaged in international collaborations, Harvard Medical School had the highest number of partnerships (total link strength = 159), followed by University of California, San Francisco (total link strength = 127) and University of Washington (total link strength = 105) (Fig. 4B).

Analysis of journals

A total of 922 academic journals contributed to publications in aging proteomics research. The top three journals based on h-index were *Journal of Proteome Research* (H-index = 34, IF 2023 = 3.8, TC = 1,924),

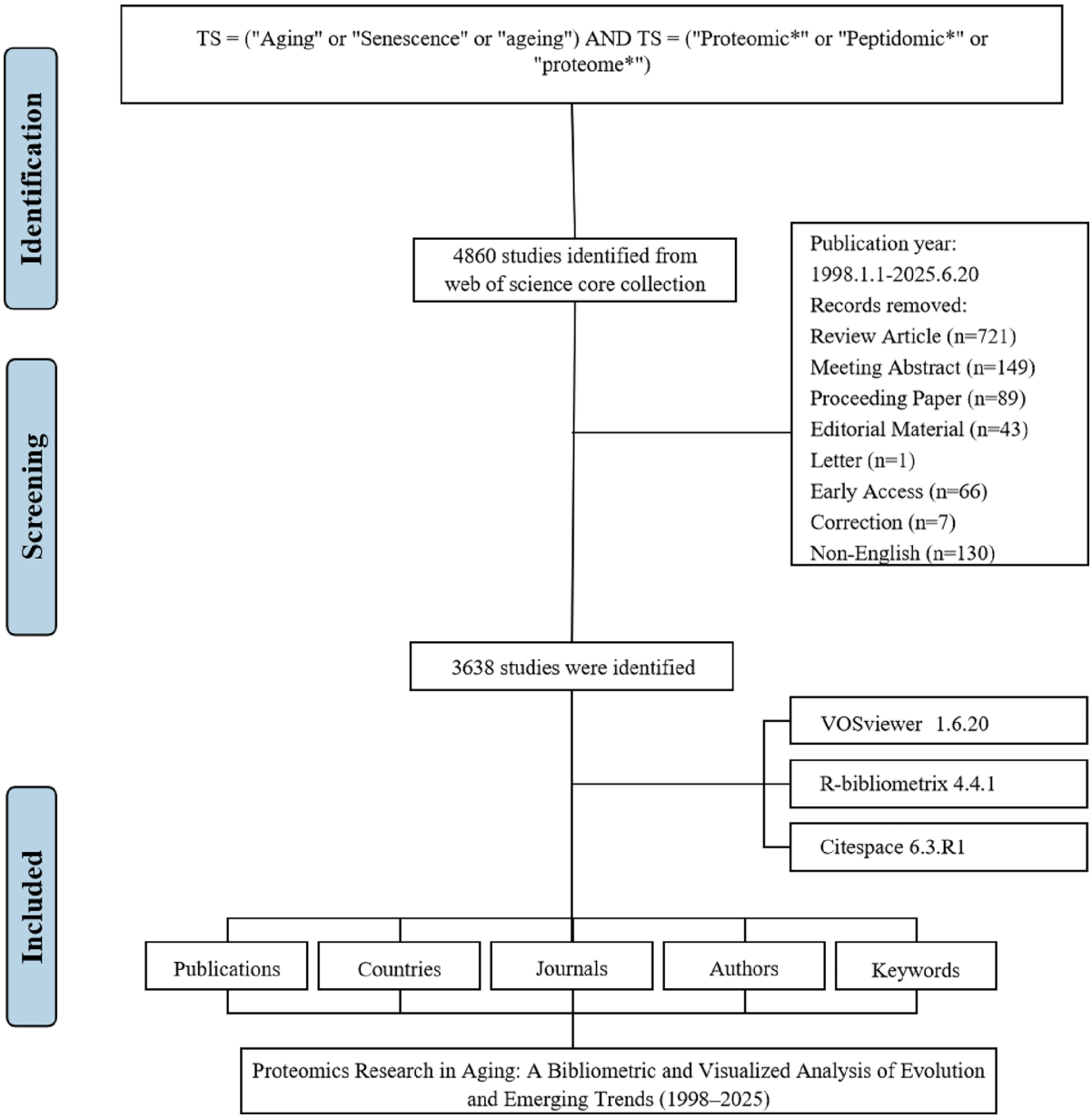


Fig. 1 Flowchart of the literature screening process

Aging Cell (H-index = 31, IF 2023 = 8.0, TC = 1,987), and *Proteomics* (H-index = 30, IF 2023 = 3.4, TC = 2,090). Other high-impact journals included *Journal of Proteomics* (H-index = 28, IF 2023 = 2.8, TC = 1,148), *PLoS One* (H-index = 28, IF 2023 = 2.9, TC = 3,176), *Scientific Reports* (H-index = 28, IF 2023 = 3.8, TC = 1,858), and *Proceedings of the National Academy of Sciences* (H-index = 27, IF 2023 = 9.4, TC = 5,500). In terms of total publications (TP), the leading journals were *Journal of Proteome Research* and *Aging Cell* (both TP = 113), followed by *International Journal of Molecular Sciences* (TP = 109), *Scientific Reports* (TP = 85), and *PLoS One* (TP = 80) (Table S2). The co-occurrence network analysis of journals, which included 127 journals with at least six occurrences, identified *Aging*

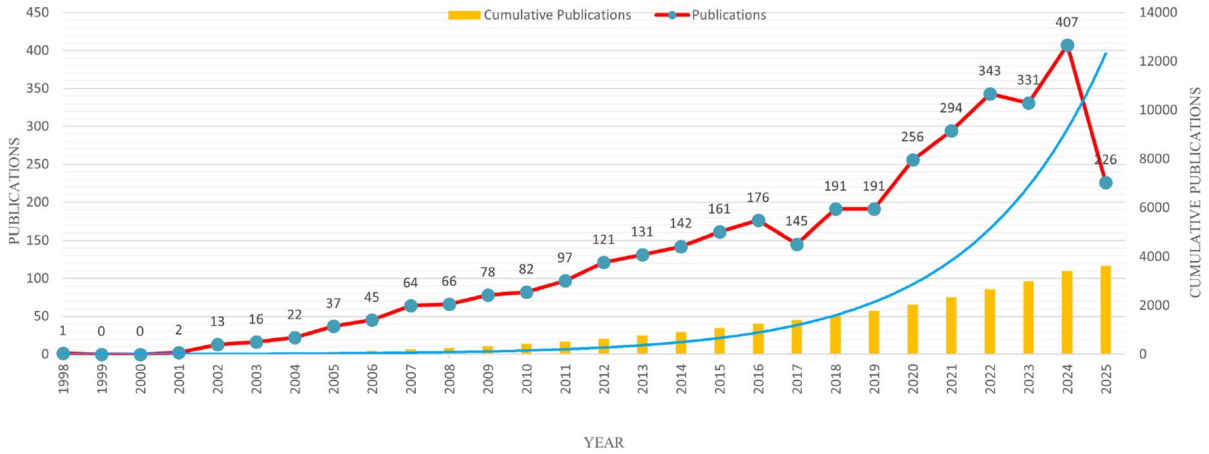


Fig. 2 Analysis of the annual number of publications

Cell (total link strength = 300), *Journal of Proteomics* (total link strength = 232), and *Journal of Proteome Research* (total link strength = 181) as the most interconnected publications (Fig. 5A). Similarly, the coupling network analysis, based on 127 journals with at least six coupling connections, highlighted *Aging Cell* (total link strength = 21,308), *Journal of Proteome Research* (total link strength = 16,421), and *International Journal of Molecular Sciences* (total link strength = 16,413) as journals sharing the strongest intellectual foundations (Fig. 5B).

Analysis of the authors

The author with the highest impact in aging proteomics research, as indicated by the h-index, was D. Allan Butterfield (H-index = 20, TC = 1,986). He was followed by Luigi Ferrucci (H-index = 17, TC = 3,667) and Kay Ohlendieck (H-index = 11, TC = 641). Regarding total publications (TP), Luigi Ferrucci led with 33 articles, followed by D. Allan Butterfield (TP = 25, TC = 1,986) and David A. Bennett (TP = 23, TC = 349). The most cited author was Luigi Ferrucci (TC = 3,667), demonstrating his significant influence in longitudinal aging studies and biomarker research. Other highly productive authors included Nathan Basisty (TP = 11, TC = 1,422), Bertrand Friguet (TP = 14, TC = 545), and Vladislav A. Petyuk (TP = 17, TC = 343) (Table S3). Among the 113 authors engaged in international collaborations with at least seven articles, Luigi Ferrucci had the highest number of collaborations (total link strength = 86), followed by David A. Bennett (total link strength = 69) and Julie A. Schneider (total link strength = 55) (Fig. 6).

Analysis of the keywords

A total of 87 high-frequency keywords were identified and categorized into five thematic clusters, each reflecting a critical aspect of aging proteomics research (Fig. 7). The red cluster (Cluster 1, 21 items) centers on protein expression and cellular senescence mechanisms, emphasizing fundamental aging processes at the molecular level. Key terms include "senescence", "gene-expression", "protein", "proteome", and “metabolism”. The green cluster (Cluster 2, 21 items) focuses on age-related diseases and neurodegeneration, particularly emphasizing brain aging and neurodegenerative conditions. Keywords in this category include "alzheimers-disease", "brain", “dementia”, “oxidative stress”, and “parkinsons-disease”. The blue cluster (Cluster 3, 19 items) emphasizes cellular processes and molecular mechanisms underlying aging, featuring terms such as “apoptosis”, “cellular senescence”, “extracellular-matrix”, and “proliferation”. The yellow cluster (Cluster 4, 18 items) pertains to stress response and longevity mechanisms, with key terms including “autophagy”, “heat-shock proteins”, “longevity”, “proteostasis”, and “caenorhabditis-elegans”. The purple cluster (Cluster 5, 8 items) focuses on

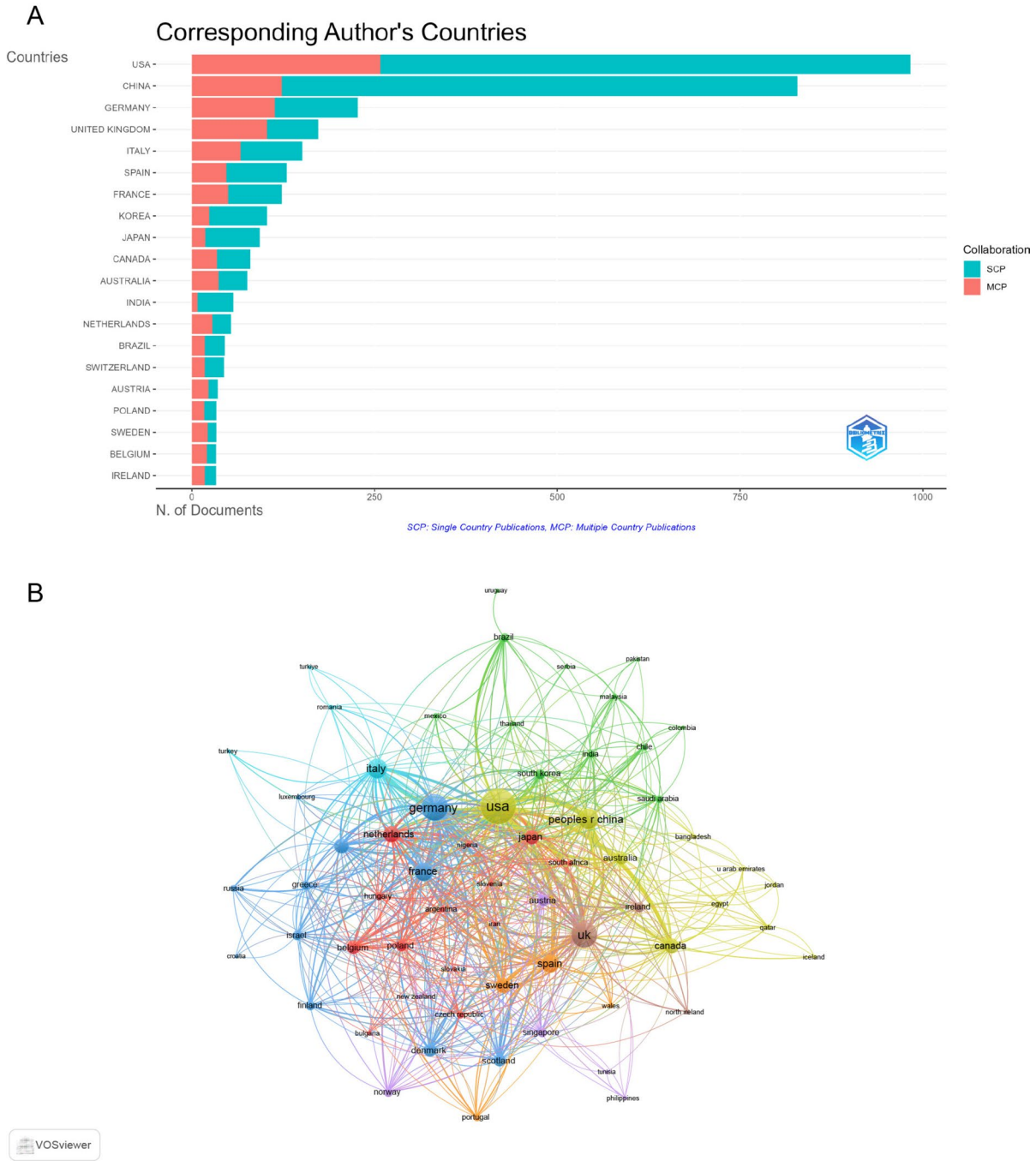


Fig. 3 Analysis of countries. **A** Distribution of corresponding author's publications by country. **B** Visualization map depicting the collaboration among different countries

advanced proteomics technologies and methodological approaches, including "mass-spectrometry", "identification", and "quantification".

The burst analysis revealed evolving research priorities (Fig. 8). The keyword with the highest burst strength was "mass spectrometry" (19.97,

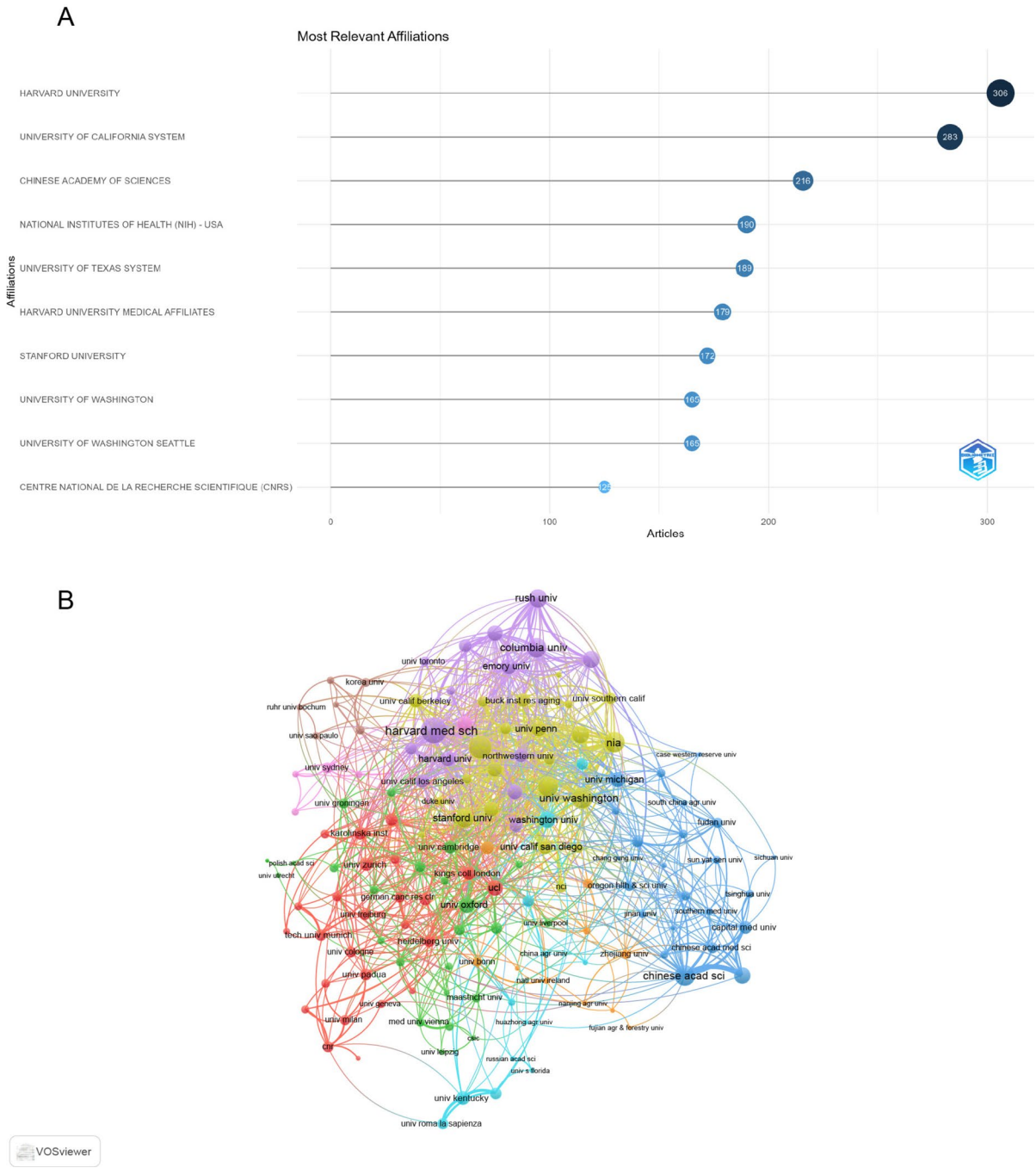
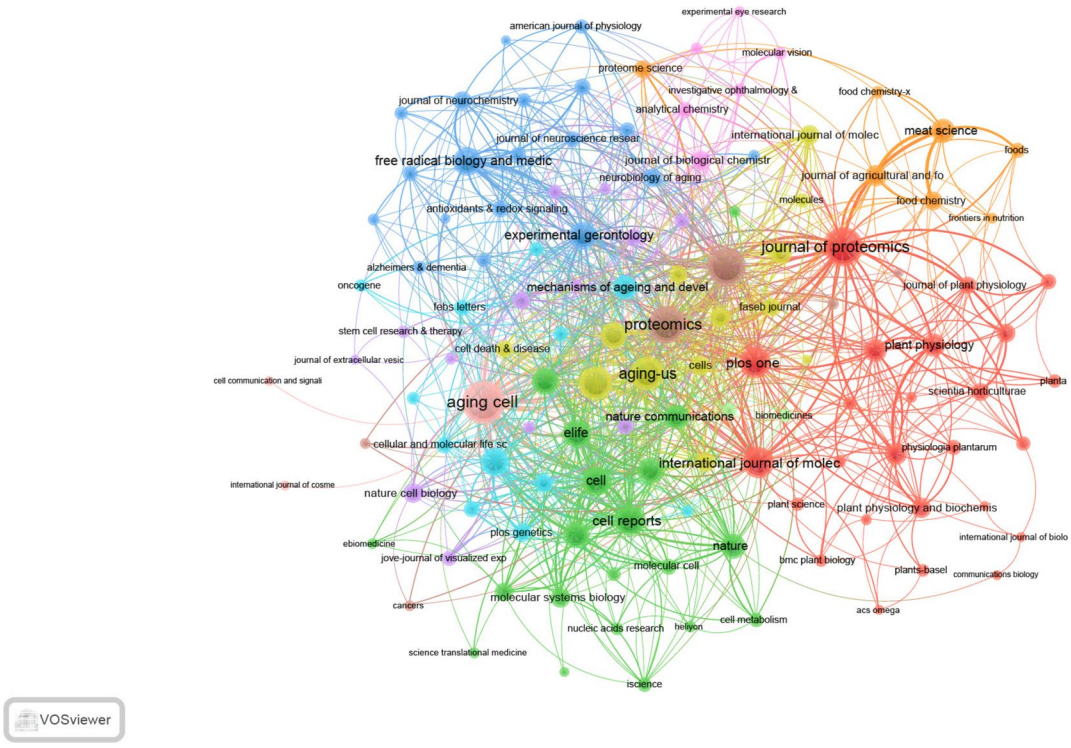


Fig. 4 Analysis of institutions. **A** Top ten institutions by article count and rank. **B** Visualization map depicting the collaboration among different institutions

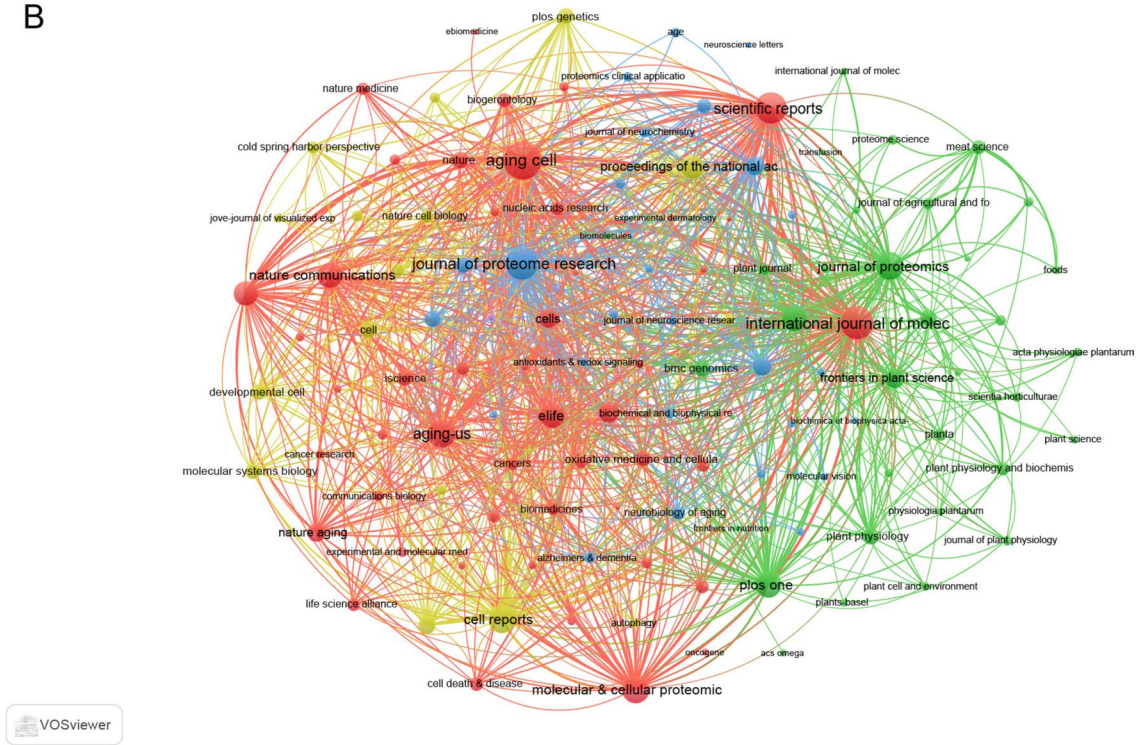
2001–2011), followed by "identification" (17.27, 2002–2009) and "in vivo" (17.27, 2003–2014). Early bursts primarily focused on establishing fundamental proteomics methodologies and basic aging mechanisms, as reflected by keywords such as "alzheimers disease brain" (13.52, 2003–2010), "proteomic identification" (11.33, 2005–2010), and "gene expression" (10.03, 2007–2014). The middle period

A



VOSviewer

B



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◂**Fig. 5** Analysis of journals. **A** Co-occurrence Network of Journals. **B** Coupling Network of Journals

emphasized model organism studies and specific aging pathways, demonstrated by keywords like "caenorhabditis elegans" (10.99, 2014–2017), "heat shock proteins" (8.61, 2014–2016), and "parkinsons disease" (11.66, 2015–2018). In more recent years, the research focus has shifted toward clinical applications and emerging therapeutic targets, as demonstrated by contemporary keywords such as "health" (9.43, 2021–2025) and "dementia" (11.19, 2022–2025), aligning with the clinical disease focus of Cluster 2, "extracellular vesicles" (11.25, 2023–2025) and "receptor" (9.62, 2023–2025), reflecting the cellular mechanism emphasis within Cluster 3, and "proteome" (9.33, 2023–2025), corresponding to the technological advances central to Cluster 5, all of which continue to show strong bursts through 2025.

Discussion

In this study, this bibliometric cluster analysis identified five research hotspots including protein expression and cellular senescence mechanisms, age-related diseases and neurodegeneration, cellular processes and molecular mechanisms, stress response and longevity mechanisms, and advanced proteomics technologies. Geographical analysis revealed that the USA ranking highest in publication output (983 publications) and citation impact (47,288 citations), indicating its significant influence on advancing research in aging proteomics (Ubaida-Mohien et al. 2021). China follows as the second most productive country with 829 publications, demonstrating the global expansion of this research field (He et al. 2019). Among institutions, Harvard University was the most prolific with 306 publications, followed by University of California System (283) and Chinese Academy of Sciences (216), highlighting their central role in aging proteomics research (Xing et al. 2024). *Journal of Proteome Research*, with an H-index of 34 and a total of 1,924 citations, stands as a leading platform for disseminating critical research findings alongside Aging Cell, which demonstrates the highest impact with significant contributions to the field (Gelfi et al. 2006).

Luigi Ferrucci from the USA has emerged as the most collaborative author with the highest total link strength (86 collaborations), contributing extensively to longitudinal aging studies and biomarker discovery research (Ferrucci et al. 2020). D. Allan Butterfield has made significant contributions to oxidative stress mechanisms in aging and neurodegeneration (Butterfield et al. 2019), while David A. Bennett has focused on cognitive aging and Alzheimer's disease proteomics (Bennett et al. 2018). The most collaborative institutional network involves Harvard Medical School, University of California San Francisco, and University of Washington, demonstrating strong inter-institutional partnerships in aging research.

The most cited article, titled "A complex secretory program orchestrated by the inflammasome controls paracrine senescence," was published in Nature Cell Biology (IF = 19.1) in 2013 and accumulated 1,598 citations, establishing fundamental understanding of senescence-associated secretory phenotype mechanisms through quantitative proteomics approaches that identified multiple SASP components mediating paracrine senescence, including TGF-β family ligands, VEGF, CCL2 and CCL20 (Acosta et al. 2013). The second most cited article, "DNA methylation GrimAge strongly predicts lifespan and healthspan," published in Aging-US in 2019 with 1,313 citations, represents breakthrough work in epigenetic aging clocks that developed DNA methylation-based estimators of plasma proteins including plasminogen activator inhibitor 1 (PAI-1) and growth differentiation factor 15, creating a composite biomarker that bridges epigenetics with protein-based aging research (Lu et al. 2019). The third most cited article, "The microglial sensome revealed by direct RNA sequencing," published in Nature Neuroscience in 2013 with 1,148 citations, provided crucial insights into microglial aging and neuroinflammation by identifying a unique cluster of transcripts encoding proteins for sensing endogenous ligands and microbes, validated through unbiased proteomic analysis alongside transcriptomic approaches (Hickman et al. 2013). These highly cited articles collectively demonstrate the integration of proteomics with other molecular approaches to understand fundamental aging mechanisms, biomarker discovery, and age-related disease pathogenesis, reflecting the field's evolution toward multi-omics approaches in aging research.

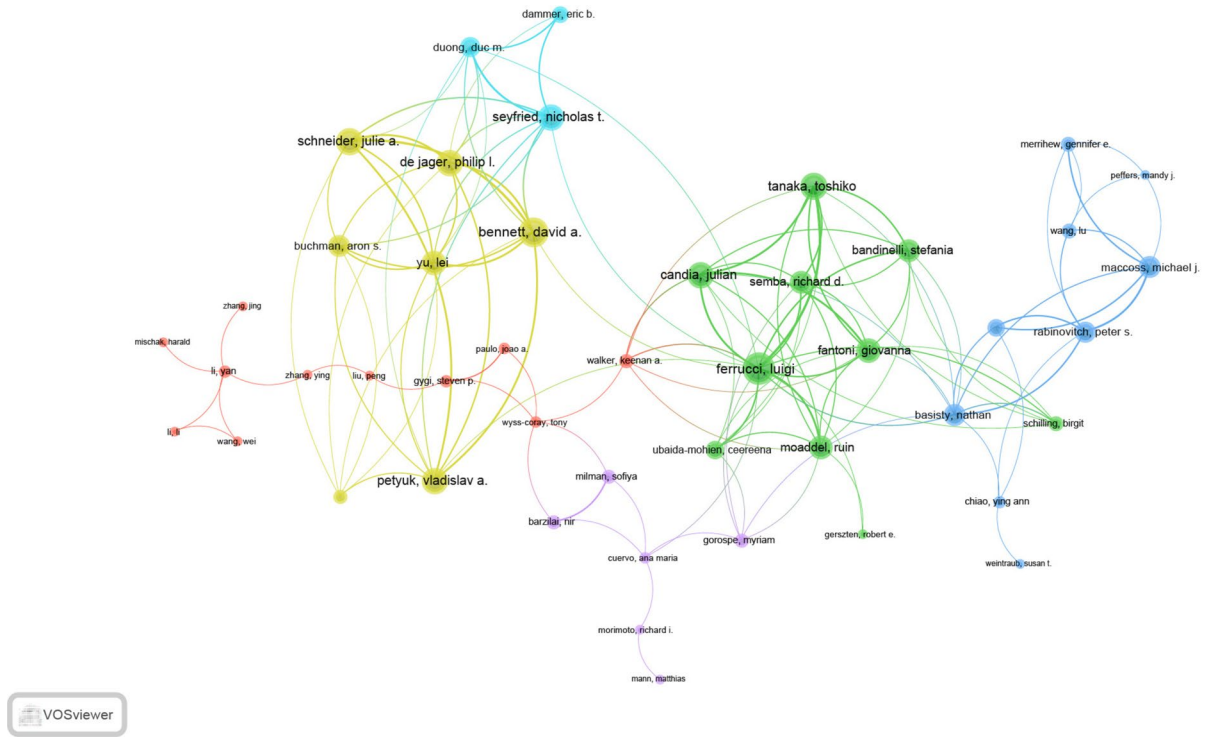

Fig. 6 Visualization map depicting the collaboration among different authors

Research hotspots

Cluster 1 (Red): Protein expression and cellular senescence mechanisms.

This cluster focuses on fundamental protein expression changes and cellular senescence pathways during aging processes. Key terms include "senescence", "gene-expression", "protein", "proteome", "metabolism", and "pathways". Research in this area has demonstrated that cellular senescence involves extensive proteomic remodeling, with significant alterations in protein synthesis, degradation, and post-translational modifications. Studies have shown that senescent cells exhibit a distinct secretory phenotype (SASP) characterized by the release of pro-inflammatory cytokines, growth factors, and matrix metalloproteinases, which contribute to tissue dysfunction and age-related pathologies (Cuollo et al. 2020). Recent proteomic analyses have identified key regulatory networks controlling senescence entry and maintenance, including p53/p21 and p16/Rb pathways, which orchestrate widespread changes in gene expression and protein abundance (Kandhaya-Pillai et al. 2023). Additionally, metabolic reprogramming during senescence involves altered mitochondrial function and energy metabolism, with proteomics revealing significant changes in glycolytic enzymes and oxidative phosphorylation complexes (Hamon et al. 2020). The identification of senescence-associated protein signatures has provided valuable biomarkers for aging research and potential therapeutic targets for age-related diseases (McHugh et al. 2025). Advanced mass spectrometry approaches have further elucidated the temporal dynamics of protein expression changes during senescence induction, revealing early and late response proteins that may serve as intervention points (Dey et al. 2023).

Cluster 2 (Green): Age-related diseases and neurodegeneration.

This cluster encompasses age-related diseases with particular emphasis on neurodegenerative conditions. Key terms include "alzheimers-disease", "brain", "dementia", "disease", "mice", "model", and

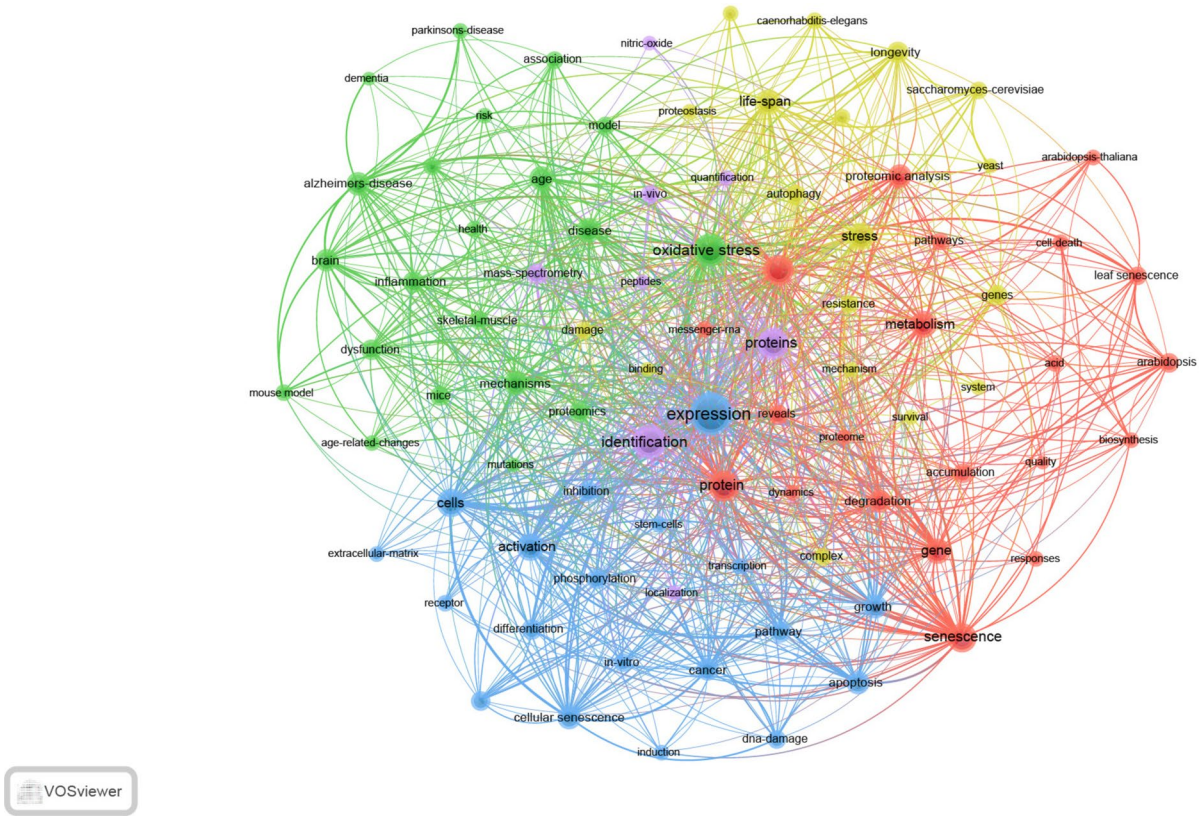

Fig. 7 Visual analysis of keyword co-occurrence network analysis

"parkinsons-disease". Proteomics has revolutionized our understanding of neurodegenerative diseases by identifying disease-specific protein signatures and pathological mechanisms. In Alzheimer's disease, large-scale proteomic studies have revealed extensive synaptic protein alterations, complement system activation, and microglial dysfunction that precede clinical symptoms (Bai et al. 2021). Tau and amyloid-β protein aggregation pathways have been extensively characterized through proteomics, leading to the identification of novel therapeutic targets and biomarkers for early disease detection (Penke et al. 2023). Parkinson's disease proteomics has highlighted α-synuclein aggregation mechanisms, mitochondrial dysfunction, and dopaminergic neuron vulnerability, providing insights into disease progression and potential neuroprotective strategies (Picca et al. 2021). Recent studies have also identified shared proteomic signatures across multiple neurodegenerative diseases, suggesting common pathological mechanisms including protein misfolding, neuroinflammation, and synaptic dysfunction (Noori et al. 2021). Furthermore, cerebrospinal fluid and plasma proteomics have enabled the development of non-invasive diagnostic tools and disease monitoring approaches, facilitating earlier intervention and personalized treatment strategies (Shama et al. 2023). Mouse models have been instrumental in validating proteomic findings and testing therapeutic interventions targeting age-related neurodegeneration.

Cluster 3 (Blue): Cellular processes and molecular mechanisms.

This cluster investigates fundamental cellular processes affected by aging, including key terms such as "activation", "apoptosis", "cells", "growth", "proliferation", and "transcription". Aging profoundly impacts cellular homeostasis through multiple interconnected pathways that regulate cell survival, proliferation, and death. Proteomic studies have revealed that apoptotic machinery undergoes significant age-related changes,

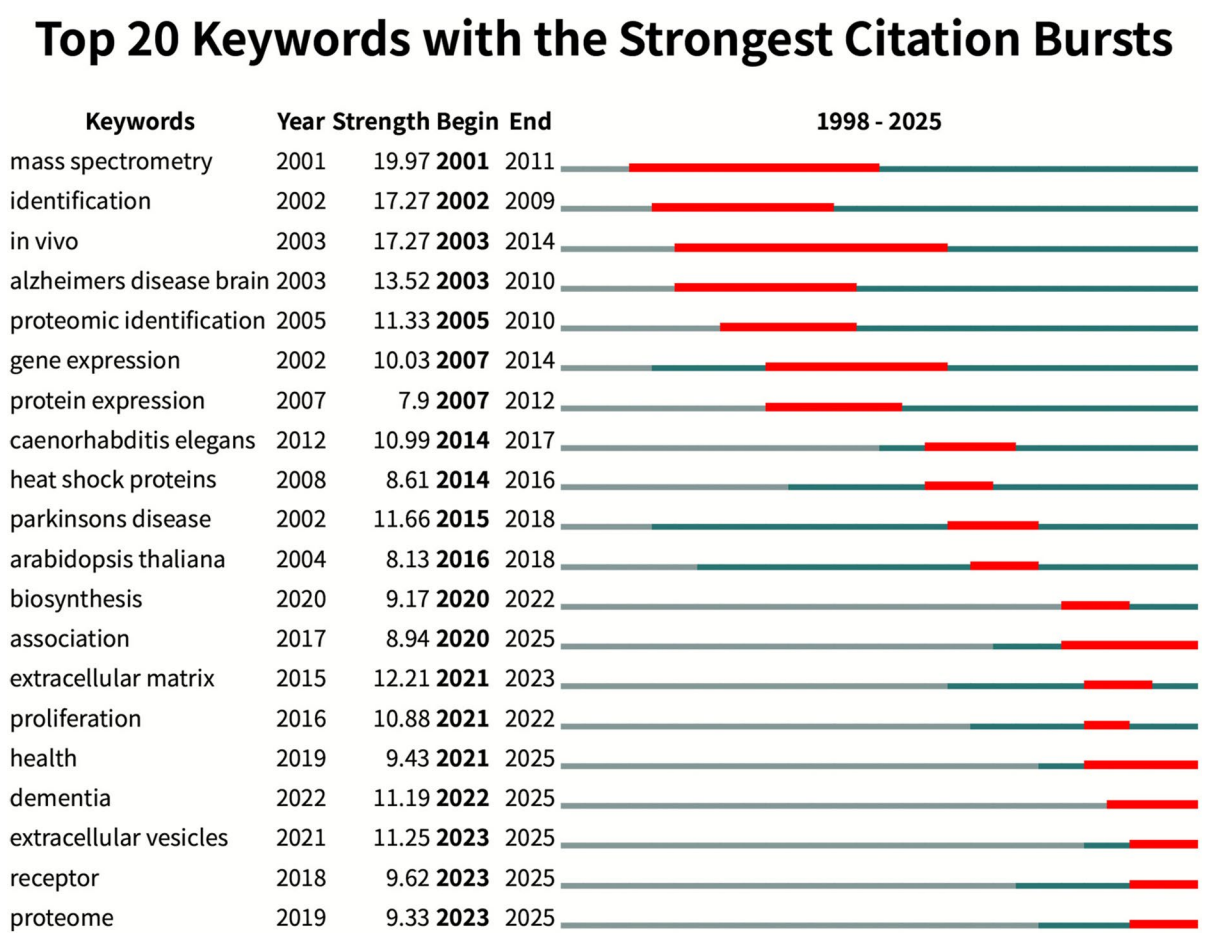

Fig. 8 Top 20 Keywords with the Strongest Citation Bursts

with altered expression of pro-apoptotic and anti-apoptotic proteins contributing to increased cell death and tissue dysfunction (Buttari et al. 2025). Growth factor signaling pathways, including insulin-like growth factor and mTOR signaling, show extensive proteomic remodeling during aging, affecting cellular metabolism, protein synthesis, and stress resistance (Ramasubbu et al. 2023). Transcriptional regulation is also heavily impacted, with age-related changes in transcription factors, chromatin remodeling complexes, and RNA processing machinery leading to widespread alterations in gene expression programs (K. Wang et al. 2022). Cell cycle regulation becomes increasingly dysregulated with age, as evidenced by proteomic changes in cyclins, cyclin-dependent kinases, and checkpoint proteins that contribute to cellular senescence and genomic instability (Kumari et al. 2021). Additionally, autophagy and protein quality control systems show significant age-related decline, with proteomic studies identifying key components of these pathways as potential therapeutic targets for promoting healthy aging (Miceli et al. 2023). The integration of proteomics with other omics approaches has provided comprehensive insights into the molecular networks governing cellular aging processes.

Cluster 4 (Yellow): Stress response and longevity mechanisms.

This cluster addresses stress response pathways and longevity mechanisms, featuring terms like "longevity", "stress", "heat-shock proteins", "caenorhabditis-elegans", "survival", and "yeast". Cellular stress response systems are critical determinants of lifespan and healthspan, with proteomics revealing how these

pathways change during aging. Heat shock proteins (HSPs) serve as molecular chaperones that maintain protein homeostasis and cellular integrity under stress conditions, and their age-related decline has been extensively characterized through proteomic approaches (Albinhassan et al. 2025). Studies in model organisms such as C. elegans and yeast have identified conserved longevity pathways, including sirtuins, FOXO transcription factors, and dietary restriction responses, that regulate lifespan through coordinated changes in protein expression (Kapahi et al. 2017). Oxidative stress response mechanisms, including antioxidant enzymes and DNA repair proteins, show significant age-related alterations that contribute to cellular damage accumulation and aging progression (Hajam et al. 2022). Proteostasis networks, encompassing protein folding, degradation, and quality control systems, become increasingly compromised with age, leading to protein aggregation and cellular dysfunction (Hipp et al. 2024). Recent proteomic studies have also identified novel stress response pathways and longevity genes that may serve as targets for interventions aimed at extending healthspan and lifespan (Bin-Jumah et al. 2022). The comparative proteomics approach across different model organisms has revealed both conserved and species-specific aging mechanisms, providing insights into the fundamental biology of aging and potential therapeutic strategies.

Cluster 5 (Purple): Advanced proteomics technologies and biomarker discovery.

This cluster focuses on technological advances and methodological approaches in aging proteomics research, including terms like "identification", "mass-spectrometry", "quantification", "proteins", and "peptides". The field has witnessed a remarkable technological evolution from early two-dimensional gel electrophoresis (2D-GE) coupled with matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry to contemporary high-resolution platforms. Early 2D-GE methods, while pioneering, were limited by dynamic range and throughput constraints, typically identifying only hundreds of abundant proteins (Kim et al. 2023). The introduction of liquid chromatography-tandem mass spectrometry (LC–MS/MS) dramatically expanded proteome coverage, while isobaric labeling techniques such as tandem mass tags (TMT) enabled multiplexed quantification across multiple aging conditions simultaneously (Z. Wang et al. 2024).

Current state-of-the-art data-independent acquisition (DIA) methods have further improved reproducibility and throughput in aging biomarker discovery studies, facilitating large-scale population-based research that was previously impractical (Kurgan et al. 2024). These technological advances have directly enabled key discoveries in aging biology. For instance, high-resolution mass spectrometry platforms facilitated the comprehensive characterization of the senescence-associated secretory phenotype (SASP), revealing its complex composition of hundreds of secreted factors that drive age-related pathologies (Samiminemati et al. 2024). The development of the "SASP Atlas"—a proteomic database cataloging secretomes from various senescent cell types—exemplifies how modern high-throughput methods have created community resources that accelerate aging research (Basisty et al. 2020).

Post-translational modification analysis has become increasingly sophisticated, with specialized enrichment and detection methods revealing age-related changes in phosphorylation, acetylation, ubiquitination, and other modifications that regulate protein function and cellular processes (Ubaida-Mohien et al. 2021). These PTM mapping capabilities have uncovered how aging affects protein regulation beyond simple abundance changes, identifying modification sites that may serve as therapeutic intervention points. Single-cell proteomics technologies are emerging as powerful tools for understanding cellular heterogeneity in aging tissues and identifying cell-type-specific aging signatures (Li et al. 2024). The integration of single-cell proteomics with transcriptomics and epigenomics is revolutionizing our ability to uncover tissue-specific aging characteristics and cellular subpopulations that may be particularly vulnerable or resistant to aging processes (Wei Zhou et al. 2025).

Additionally, targeted proteomics approaches using selected reaction monitoring (SRM) and parallel reaction monitoring (PRM) have enabled precise quantification of candidate aging biomarkers in clinical samples, bridging the gap between discovery and clinical validation(Son et al. 2024). Workflow innovations including sample preparation methods such as single-pot solid-phase-enhanced sample preparation

(SP3), suspension trapping (S-Trap), and the AccelerOme platform have dramatically improved sensitivity, reproducibility, and throughput while reducing sample input requirements and processing time. These advances have been particularly impactful for aging research involving precious clinical specimens and have enabled the processing of large cohort studies that provide statistical power for biomarker validation. The integration of proteomics with other omics technologies, including genomics, transcriptomics, and metabolomics, has provided systems-level insights into aging processes and facilitated the development of comprehensive aging biomarker panels for clinical applications.

Translating technological advances into biological insights

The methodological innovations in mass spectrometry-based proteomics have generated transformative biological insights that would have been impossible with earlier technologies. Improved sensitivity and throughput have enabled the construction of comprehensive proteomic atlases that serve as community resources. The SASP Atlas, for example, represents a landmark achievement made possible by modern high-throughput workflows (Basisty et al. 2020). This resource systematically catalogs the secretomes of multiple senescent cell types, revealing both common and context-specific SASP components. Such comprehensive mapping has refined our understanding of how senescent cells communicate with their microenvironment and has identified previously unknown paracrine factors that may serve as aging biomarkers or therapeutic targets.

Advanced peptide enrichment strategies, combined with high-resolution mass spectrometry, have enabled deep coverage of post-translational modifications during aging. These approaches revealed that aging is associated not only with changes in protein abundance but also with extensive remodeling of the "PTM landscape"—particularly in phosphorylation networks regulating cell cycle, DNA damage response, and metabolic pathways (Hamon et al. 2020). The ability to quantify thousands of phosphorylation sites simultaneously has uncovered kinase-substrate relationships disrupted during aging, providing mechanistic insights into senescence signaling cascades and identifying potential druggable nodes in these pathways.

Automation and miniaturization technologies such as SP3, S-Trap, and AccelerOme have democratized proteomics by reducing sample requirements and processing time, enabling studies with limited clinical specimens such as cerebrospinal fluid and plasma from aging cohorts (Shama et al. 2023). These advances have directly facilitated longitudinal aging studies that track proteomic changes over time within individuals, revealing temporal dynamics of aging that cross-sectional studies could not capture. For instance, longitudinal plasma proteomics in the Baltimore Longitudinal Study of Aging identified proteins with non-linear trajectories that mark transitions between different phases of aging, information critical for timing interventions appropriately (Ferrucci et al. 2020).

The integration of label-free quantification with DIA acquisition has enabled large-scale, reproducible comparisons across hundreds of samples, a capability essential for discovering and validating aging biomarkers in diverse populations (Sun et al. 2024). This technological convergence has revealed that proteomic aging signatures show both universal and population-specific features, with implications for personalized approaches to healthy aging. Collectively, these workflow innovations have transformed aging proteomics from a descriptive science focused on cataloging changes into a mechanistic discipline capable of revealing causal relationships and guiding therapeutic development.

Evolution of study trends

Citation burst analysis reveals the evolving landscape of aging proteomics research, demonstrating a clear progression from foundational methodological development to advanced disease-specific applications and emerging therapeutic targets. From 2001 to 2014, research was dominated by fundamental proteomics technologies and basic aging mechanisms. Keywords such as "mass spectrometry" (2001–2011), "identification" (2002–2009), and "in vivo" (2003–2014) highlight the establishment of robust analytical platforms for aging research (Aebersold et al. 2016). During this period, foundational studies focused on developing reliable methods for protein identification

and quantification in aging models, with particular emphasis on brain aging and Alzheimer's disease research, as evidenced by "alzheimers disease brain" (2003–2010) and "proteomic identification" (2005–2010) (Hondius et al. 2016).

The period from 2014 to 2020 marked a transition toward model organism studies and specific aging pathways. Citation bursts for "caenorhabditis elegans" (2014–2017), "heat shock proteins" (2014–2016), "parkinsons disease" (2015–2018), and "arabidopsis thaliana" (2016–2018) indicate increased focus on conserved aging mechanisms across different species and neurodegenerative diseases (Pitt et al. 2015). This era emphasized understanding fundamental aging processes through well-characterized model systems. The emergence of "biosynthesis" (2020–2022) during the transition period reflected growing interest in protein synthesis and metabolic changes during aging (Ottens et al. 2021).

Since 2020, research has shifted toward clinical translation and emerging therapeutic targets. Keywords including "association" (2020–2025), "extracellular matrix" (2021–2023), "health" (2021–2025), and "dementia" (2022–2025) reflect the field's movement toward population-based studies and clinical applications (Anstey et al. 2022). Most notably, recent bursts in "extracellular vesicles" (2023–2025), "receptor" (2023–2025), and "proteome" (2023–2025) highlight cutting-edge areas focusing on intercellular communication, precision medicine, and comprehensive proteomic profiling for aging biomarker discovery (Xie et al. 2025).

From proteomics discovery to therapeutic development

The proteomic discoveries highlighted in this bibliometric analysis are increasingly being translated into therapeutic strategies targeting aging and age-related diseases. The comprehensive characterization of cellular senescence mechanisms through proteomics has directly enabled the development of two major therapeutic approaches: senolytics (drugs that selectively eliminate senescent cells) and senomorphics (agents that suppress the harmful SASP without killing senescent cells) (McHugh et al. 2025). Proteomic profiling has identified key SASP components such as pro-inflammatory cytokines, matrix metalloproteinases, and growth factors that drive age-related tissue dysfunction, providing a rational basis for senomorphic drug design aimed at neutralizing these specific factors.

Recent proteomic studies have revealed novel senescence regulators that represent promising therapeutic targets. For example, quantitative proteomics identified FRMD6 as a critical mediator of oncogene-induced senescence whose depletion can bypass senescence barriers (Park et al. 2024). Such discoveries expand the repertoire of potential senolytic targets beyond the well-studied BCL-2 family proteins. Similarly, proteomic characterization of the senescent cell surface proteome has identified membrane proteins specifically enriched in senescent cells, offering opportunities for targeted drug delivery or immunotherapeutic approaches that could selectively eliminate senescent cells while sparing healthy tissue.

The translation of proteomic findings into clinical interventions increasingly relies on advanced techniques such as Cellular Thermal Shift Assay coupled with mass spectrometry (CETSA-MS), which enables proteome-wide assessment of drug-target engagement in living cells (Thikekar et al. 2023). This approach bridges the gap between target identification and drug validation by confirming that candidate senolytic or senomorphic compounds physically interact with their intended protein targets at therapeutically relevant concentrations. CETSA-MS has been particularly valuable for validating the mechanism of action of novel aging-targeted drugs and for identifying off-target interactions that may contribute to side effects.

Furthermore, proteomic approaches are being applied to stratify patient populations for aging-targeted interventions. Plasma proteomic profiling can identify individuals with elevated senescence burdens or specific SASP signatures who may benefit most from senolytic therapy (Ferrucci et al. 2020). This precision medicine approach, enabled by the high-throughput proteomic platforms described in Cluster 5, represents a paradigm shift from one-size-fits-all interventions toward personalized strategies for promoting healthy longevity. As aging therapeutics advance toward clinical translation, proteomics will continue to play essential roles in target discovery, drug development, patient stratification, and pharmacodynamic monitoring—ultimately accelerating the path from basic aging research to interventions that extend human healthspan.

Strengths and limitations

The main strength of this study lies in its comprehensive coverage of the aging proteomics field, analyzing 3,638 publications across multiple dimensions. The combination of various bibliometric tools provides robust insights into research trends and emerging directions. However, several limitations should be noted. First, our analysis relied solely on the WoSCC database, potentially missing relevant publications indexed elsewhere. Second, the focus on English-language publications may underrepresent contributions from non-English-speaking regions. Third, citation metrics for recent publications may be underestimated due to the natural lag in citation accumulation. Fourth, as a bibliometric analysis, this study focuses on publication metadata and high-level research trends rather than protein-level data. While our approach provides valuable insights into the field's structure and evolution, a complementary meta-analysis extracting and synthesizing protein-level findings from individual studies would be needed to identify consensus aging biomarkers and validate mechanistic pathways—representing an important direction for future research.

Conclusion

This bibliometric analysis based on cluster analysis identified five research hotspots in aging proteomics including protein expression and cellular senescence mechanisms, age-related diseases and neurodegeneration, cellular processes and molecular mechanisms, stress response and longevity mechanisms, and advanced proteomics technologies and biomarker discovery. There is a clear temporal progression among the strongest citation bursts, with the period from 2001–2014 primarily concentrated on establishing fundamental proteomics methodologies and basic aging mechanisms. From 2014–2020, research transitioned toward model organism studies and specific aging pathways. Since 2020, the field has shifted toward clinical translation and emerging therapeutic targets, focusing on extracellular vesicles, dementia research, and comprehensive proteome profiling for precision medicine applications in aging and age-related diseases.

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