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Cellular Senescence and Anti-Aging Strategies in Aesthetic Medicine: A Bibliometric Analysis and Brief Review

Huilan Zheng[1], Jingping Wu[2], Jinhong Feng[2], Hongbin Cheng[3]

[1]School of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan Province, 610075, People's Republic of China; [2]Department of Medical Cosmetology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan Province, 610075, People's Republic of China; [3]Department of Dermatology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan Province, 610075, People's Republic of China

Correspondence: Hongbin Cheng, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu University of Traditional Chinese Medicine, No. 39, Shierqiao Road, Jinniu District, Chengdu, Sichuan Province, 610075, People's Republic of China, Email chenghongbin@cdutcm.edu.cn

Background: Skin aging is the most obvious feature of human aging, and delaying aging has become a hot and difficult research topic in aesthetic medicine. The accumulation of dysfunctional senescent cells is one of the important mechanisms of skin aging, based on which a series of anti-aging strategies have been generated. In this paper, from the perspective of cellular senescence, we utilize bibliometrics and research review to explore the research hotspots and trends in this field, with a view to providing references for skin health and aesthetic medicine.

Methods: We obtained literature related to this field from the Web of Science Core Collection database from 1994 to 2024. Bibliometrix packages in R, CiteSpace, VOSviewer, Origin, and Scimago Graphica were utilized for data mining and visualization.

Results: A total of 2,796 documents were included in the analysis. The overall trend of publications showed a continuous and rapid increase from 2016–2023, but the total citations improved poorly over time. In this field, *Journal of Cosmetic Dermatology, Journal of Investigative Dermatology, Experimental Gerontology* are core journals. Kim J, Lee JH, Lee S, Rattan SIS, Chung JH and Kim JH are the core authors in this field. Seoul National University is the first in terms of publications. Korea is the country with the most publications, but USA has the most total citations. Top 10 keywords include: gene-expression, skin, cellular senescence, cell, oxidative stress, antioxidants, in vitro, fibroblasts, mechanism, cancer. Current research trends are focused on neurodegeneration, skin rejuvenation, molecular docking, fibrosis, wound healing, SASP, skin barrier, and antioxidants. The core literature and references reflect topics such as the major molecular pathways in the aging process, and the relationship with tumors.

Conclusion: This field of research has been rapidly rising in recent years. Relevant research hotspots focus on oxidative stress, fibroblasts, and senescence-associated secretory phenotype. Anti-aging strategies targeting cellular senescence hold great promise, including removal of senescent cells or attenuation of SASP factors, corresponding to senolytics and senomorphics therapies, respectively.

Keywords: cellular senescence, skin aging, aesthetic medicine, senolytic, anti-aging

Introduction

Aging and the characteristics associated with it have received a great deal of attention from researchers due to the aging of the population and the increasing emphasis on physical appearance.[1] By 2030, one in six people worldwide will be 60 or older, according to the World Health Organization (WHO) 2022. By 2050, this percentage will increase to 22%, or 2.1 billion people. At the same time, the number of people seeking aesthetic treatments continues to grow, and the concept of "better/slower aging" has been proposed.[2] The essence of aging is the progressive functional decline of various organ systems of the organism, and structural and functional changes in the skin are the most obvious features of human aging.[3] Skin senescence not only affects the appearance, but is also closely related to the occurrence and development of many skin diseases such as skin tumors, skin pigmentation, and so on.[4,5] Aging is inevitable, and skin

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problems are common in older adults. A systematic review examined the prevalence and incidence of more than 20 skin conditions in people aged 65 years and older.[6] Of these, the most common include fungal infections (14.3%–64%), benign skin tumors (1.7%–74.5%), and others. Elderly people have more fragile skin and are more susceptible to pathogenic microorganisms.

Cellular senescence is the core regulatory mechanism of aging, and one of the most important etiological factors of skin aging.[7,8] The accumulation of dysfunctional senescent cells reduces the repair and regenerative capacity of tissues, leading to impaired tissue homeostasis, integrity, and function, which has deleterious effects on the skin and contributes to a wide range of senescence-related skin diseases.[9] To address the mechanisms of skin aging, researchers have proposed a series of anti-aging strategies. This is also in line with the current strong growth of the aesthetic medicine market. These include medical interventions such as the application of antioxidants, the cell regulators, invasive procedures, and skin care, as well as lifestyle modifications such as sun protection, dietary control, and physical activity.[10–12] The aim is to protect skin cells from oxidative stress and inflammatory responses, and to promote skin cell proliferation and differentiation, thereby promoting homeostasis and slowing down skin aging. Currently, anti-aging strategies that target cellular senescence have demonstrated clinical efficacy. Senolytic therapy reduced senescent cells in the skin of patients with diabetic kidney disease.[13] In addition, topical application of a combination of niacinamide and hyaluronic acid senomorphic therapy has been found to improve facial wrinkles, smoothness, radiance complexion, and other skin conditions in women.[14] Therefore, in-depth study of the mechanisms of skin aging and exploration of effective anti-aging strategies have become important issues in the fields of dermatology and aesthetic medicine.

Bibliometrics can be used to reveal the distributional characteristics, internal patterns and structural relationships of the literature through quantitative statistics and visual analysis of academic publications in a certain field.[15,16] This research method improves the intuition and interpretability of the analysis, and provides data support and theoretical basis for scientific research, academic evaluation, etc. Several researchers have already explored the field of aging with this approach in the past. Sun et al summarized the research related to photoaging from 2000 to 2020.[17] Li et al provided an overall overview of the research on cellular aging without focusing on the cosmetic aspect of skin.[18] There are also researchers who have combined cellular senescence and osteoarthritis.[19,20] On a more refined note, Yue et al performed a bibliometric analysis about the senescence-associated secretory phenotype (SASP) on oral immune homeostasis.[21] In addition, there have been review studies investigating skin senescence in the context of cellular senescence as well as senotherapeutics.[22,23] Our work extends and highlights this idea and is the first study to comprehensively analyze this field from a bibliometric perspective. Thus, this paper will explore the mechanism of skin aging and the current research hotspots and trends in anti-aging strategies from the perspective of cellular aging, with a view to providing scientific basis and reference for skin health and aesthetic medicine. Through in-depth study of the mechanisms of cellular senescence and skin aging, it helps researchers to better understand the nature of skin aging and helps to discover more updated anti-aging targets.

Material and Methods

Data Collection

Bibliographic data were sourced from the Web of Science Core Collection database (WoSCC, Clarivate Analytics),[24,25] which includes editions of Social Sciences Citation Index and Science Citation Index Expand. To avoid bias caused by daily database updates, all WoSCC screenings were carried out on May 19, 2024, for the period from 1994-01-01 to 2024-05-19. The search strategy was [(TS=(((“cellular senescence”) OR (“intrinsic aging”) OR (“extrinsic aging”) OR (“senescent cell*”) OR (“Senescence-Associated Secretory Phenotype”) OR (“SASP”) OR (“anti-aging”) OR (“Senotherapeutic*”) OR (“Seno-Therapeutic”) OR (“Geroprotector*”) OR (“Senoptosis”) OR (“Senoptotic*”) OR (“Senostatic”) OR (“Senolytic*”) OR (“Senomorphics*”)) AND ((“skin”) OR (“aesthetic*”) OR (“cosmetic*”) OR (“beauty”))))]. The above keywords were curated from the Medical Subject Headings (MeSH) database (https://www.ncbi.nlm.nih.gov/mesh/). Then “articles” and “reviews” were selected as document types and “English” was selected as document language when utilized the filter function.

Data Analyzes

Data collection and pre-processing were completed by 2 researchers independently. In case of disagreement on the nesting of the documents, the decision was made by the 3rd researcher. The biblioshiny website[26] in the bibliometrix R-package was used to check duplicates (n=0), frequency statistics and plot. The relevant information was summarized in a table using Microsoft Excel (version 2304 Build 16.0.16327.20200). The journal information was acquired from the 2023 Journal Citation Report (Clarivate Analytics, Philadelphia, PA, United States). The keywords merging was carried out by thesaurus_terms.txt file (VOSviewer software). For bibliometric and visual analyzes following software were used: VOSviewer (version 1.6.19, van Eck and Waltman, 2010,[27,28]), Origin (version 2022) and SCImago Graphica (version 1.0.26, Yusef Hassan-Montero, V. Guerrero-Bote, and Félix De-Moya-Anegón,[29,30]).

Results

General Analysis of Publication Status

Through database search, a total of 2796 documents were included (Figure 1A). The trend of publications in this field can be divided into 3 parts (Figure 1B): the growth of publications from 1994–2014 was relatively stable, the first rapid increase was seen in 2014–2016, and 2016–2023 showed a continuous rapid increase. The highest number of publications was reached in 2023 (356). At the same time, there is a significant increase in the publication of review-type articles. In average citations per year, the most citations are in 1995 (23.3), 1997 (13.8) and 2001 (8.2) ranked 2nd and 3rd. As can be seen from the figure, although the number of publications is increasing, the total number of citations is not satisfied. We consider that more original research of high quality deserves to be carried out in this field.

Analysis of Journals and Their Influence

A total of 777 publication sources were found in this study. Bradford's Law showed 22 major core journals (Figure 2A). Among them, *Journal of Cosmetic Dermatology* was the 1st in terms of number of publications (152), *International Journal of Molecular Sciences* was the 2nd (97), and the 3rd was *Molecules* (69) (Figure 2B). Among them, *Journal of Cosmetic Dermatology* is an international academic journal focusing on cosmetic dermatology, founded in 2001. It is the official journal of the International Academy of Cosmetic Dermatology (IACD) and the Canadian Association of Aesthetic Medicine

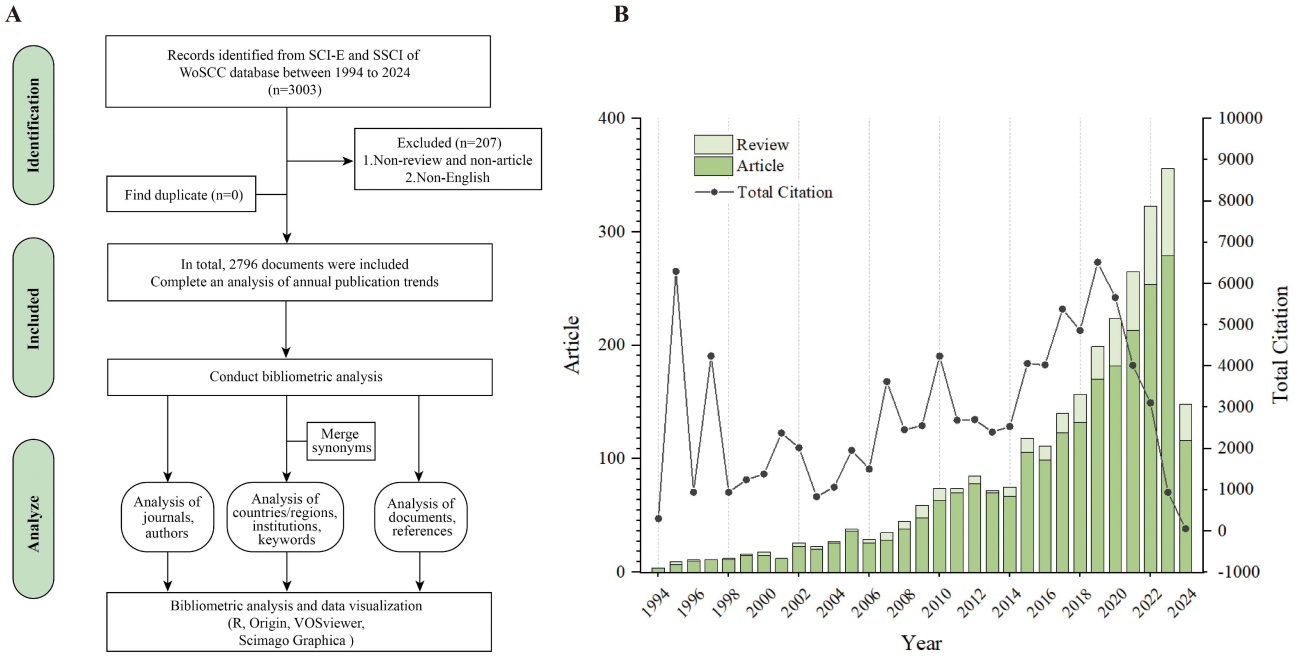

Figure 1 Technical routes and publication trends. (**A**) Flowchart for literature screening, exclusion, inclusion and analysis. (**B**) Trends in annual scientific production and total citations.

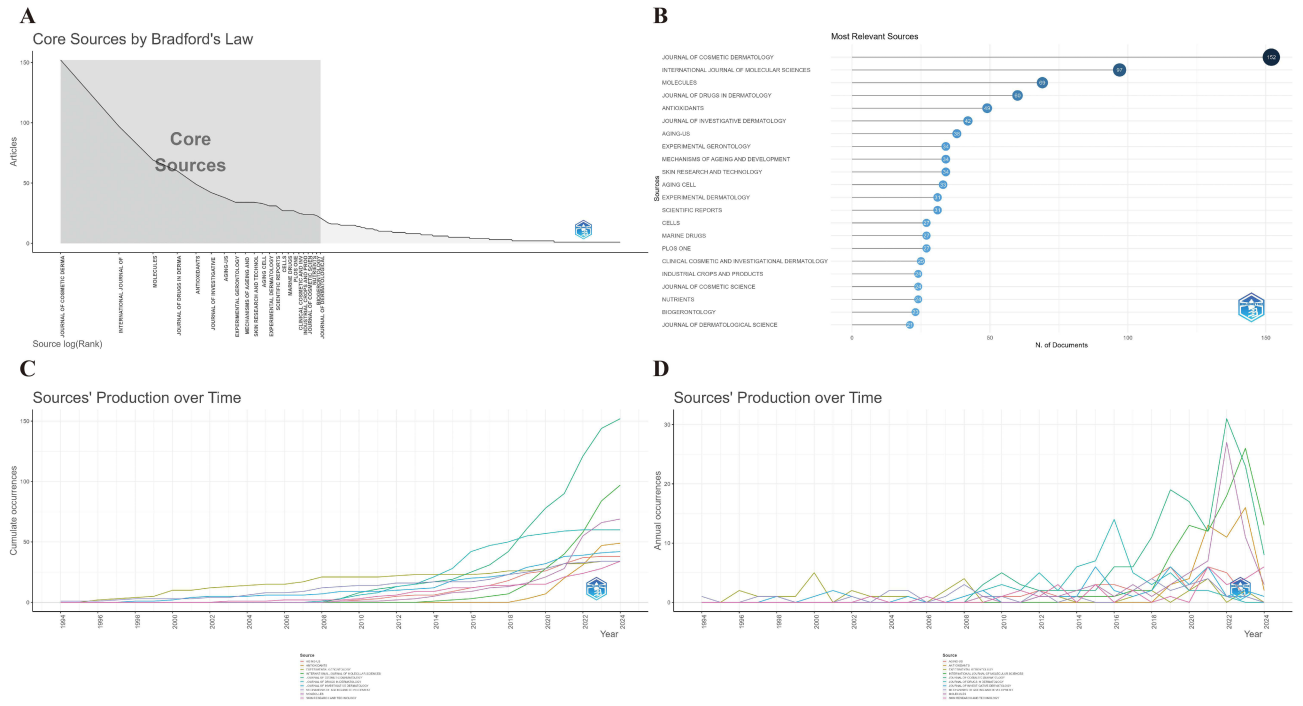

Figure 2 Core journals and journal publication trends. (**A**) Core journals analyzed through Bradford's Law. (**B**) Publications in the top 22 core journals. (**C**) Cumulative publication trends in the top 10 core journals. (**D**) Annual publication trends in the top 10 core journals.

(CAAM). It publishes in the fields of skin anti-aging, laser treatments, filler injections, skin care, and many others. Among the locally cited journals, *Journal of Investigative Dermatology* is far ahead in citations (4,363), *Nature* is 2nd (2,607), *Proceedings of the National Academy of Sciences of the United States of America* is 3rd (2,420). *Journal of Investigative Dermatology* is an international dermatology journal, founded in 1938, that publishes original articles related to skin biology and skin diseases. It covers a wide range of research areas, including skin development, immunology, genetics, cell biology, and clinical research. Analysis of the journals' impact revealed (Table 1) that *Journal of Investigative Dermatology* had the

Table 1 Top 10 Core Journals and Influence

Rank	Journal	Total Citations	Article Count	H-Index	G-Index	Journal Citation Reports (2023)	Impact Factor (2023)
1	Proceedings of The National Academy of Sciences of The United States of America	8576	14	14	14	Q1	9.4
2	Cell	4344	3	3	3	Q1	45.5
3	Journal of Investigative Dermatology	2017	42	27	42	Q1	5.7
4	Ageing Research Reviews	1869	15	15	15	Q1	12.5
5	Journal of Cosmetic Dermatology	1782	152	19	36	Q3	2.3
6	Mechanisms of Ageing and Development	1760	34	17	34	Q2	5.3
7	International Journal of Molecular Sciences	1746	97	21	39	Q1	4.9
8	Molecules	1668	69	20	39	Q2	4.2
9	Genes & Development	1642	6	6	6	Q1	7.5
10	Experimental Gerontology	1626	34	21	34	Q2	3.3

highest h-index (27), followed by *Experimental Gerontology* (21) and *International Journal of Molecular Sciences* (21). As can be seen from the production over time of the journals (Figure 2C), *Journal of Cosmetic Dermatology* has continued to rise since reaching 42 publications in 2018 and has 152 publications until 2024. *International Journal of Molecular Sciences* has also started to grow rapidly in this field since it published 7 articles in 2018 and has already accumulated 97 publications by 2024. As can be seen in the annual publications in the last 3 years (Figure 2D), 2022–2023 is a period of rapid publications in the core journals, with *Journal of Cosmetic Dermatology* publishing 31 in 2022 and *Molecules* publishing 27 in 2022.Besides, *International Journal of Molecular Sciences* published 26 articles in 2023.

Analysis of Authors and Their Production

From this study, a total of 12,355 authors were found in this field. Sankey diagram shows the top 20 authors by institution and country (Figure 3A). Korea has the highest number of authors in this field, followed by China. In the analysis of the core authors, Kim J is the 1st in terms of publications (45), Lee JH is the 2nd (41), and Lee S is the 3rd (31). As seen in Figure 3B, authors in this field are relatively decentralized, forming many core groups. Among the most locally cited authors, Campisi J reaped the most local citations (533), Rubelj I is 2nd (341), and Medrano EE is 3rd (337). Based on the annual publication trend of the top 20 authors (Figure 3C), Lee J, Chung JH and Kim KH focused on the field the earliest. Lee JH and Lee J harvested the most total citations in 2020. According to the influence of the top 10 authors (Table 2), Rattan SIS has the 1st h-index (19), while Chung JH is the 2nd (16). In addition, there are a total of three with h-index of 15: Kim J, Kim JH, and Lee S. These are the core authors in the field.

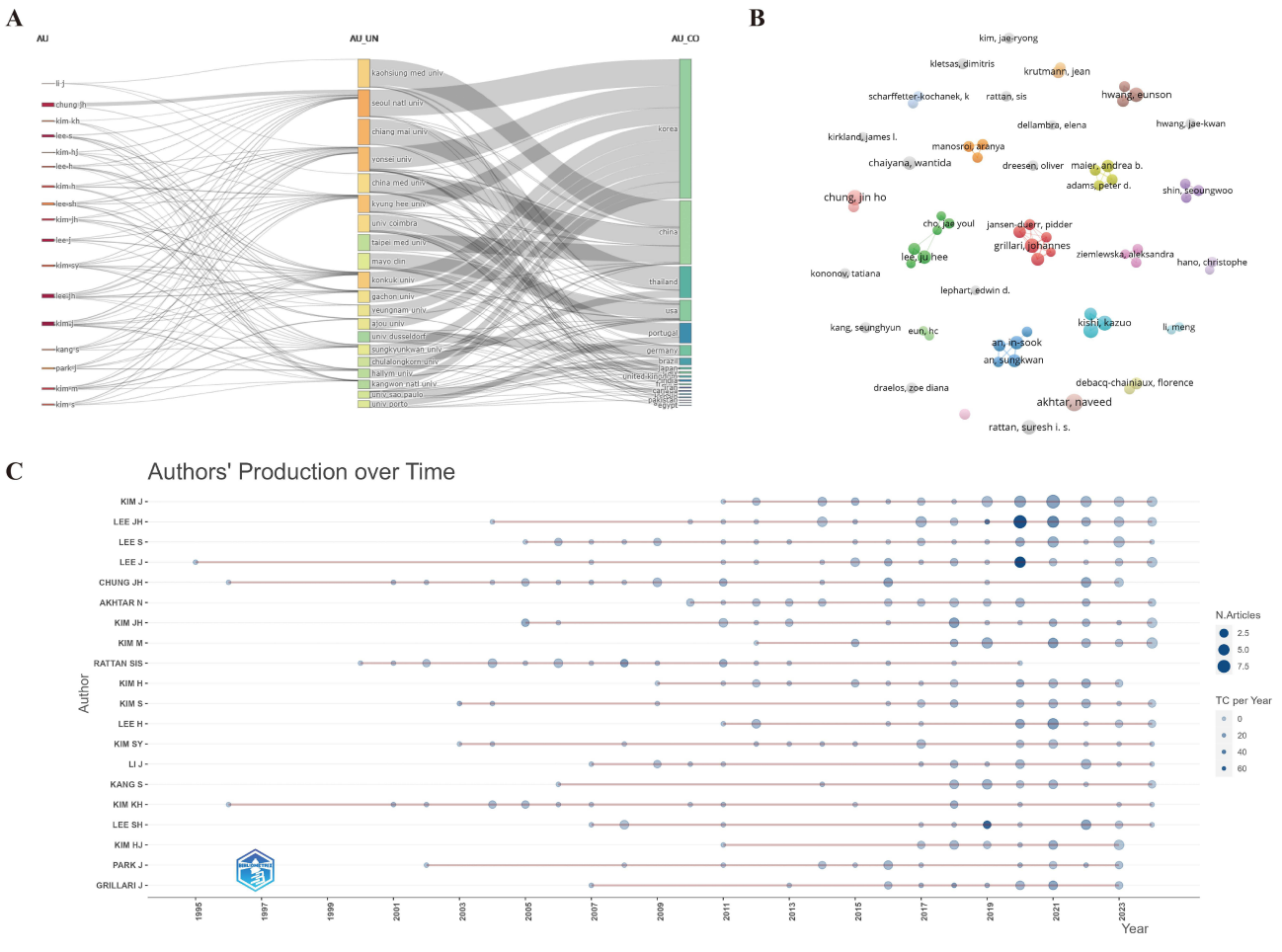

Figure 3 Core authors and authors' annual publications. (**A**) Sankey diagram of the top 20 authors. (**B**) Cluster analysis of core authors. (**C**) Annual publication trends of the top 20 authors.

Table 2 Top 10 Core Authors and Influence

Rank	Author	Article Count	h_index	g_index	Total Citations	Publication Start Year
1	Campisi J	11	10	11	7825	1995
2	Rattan SIS	22	19	22	1189	2000
3	Scharffetter-Kochanek K	14	12	14	1170	1998
4	Wlaschek M	14	12	14	1170	1998
5	Chung JH	26	16	26	1136	1996
6	Lee JH	41	14	32	1050	2004
7	Lee J	28	13	27	779	1995
8	Kim KH	17	12	17	752	1996
9	Krutmann J	11	11	11	746	2008
10	Kim JH	25	15	25	709	2005

Analysis of Countries/Regions, Institutions, and Their Cooperation

By analyzing the core institutions, it is seen that Seoul National University has the 1st number of publications (116), Chiang Mai University is the 2nd (100), and Yonsei University is the 3rd (89). According to the analysis of the

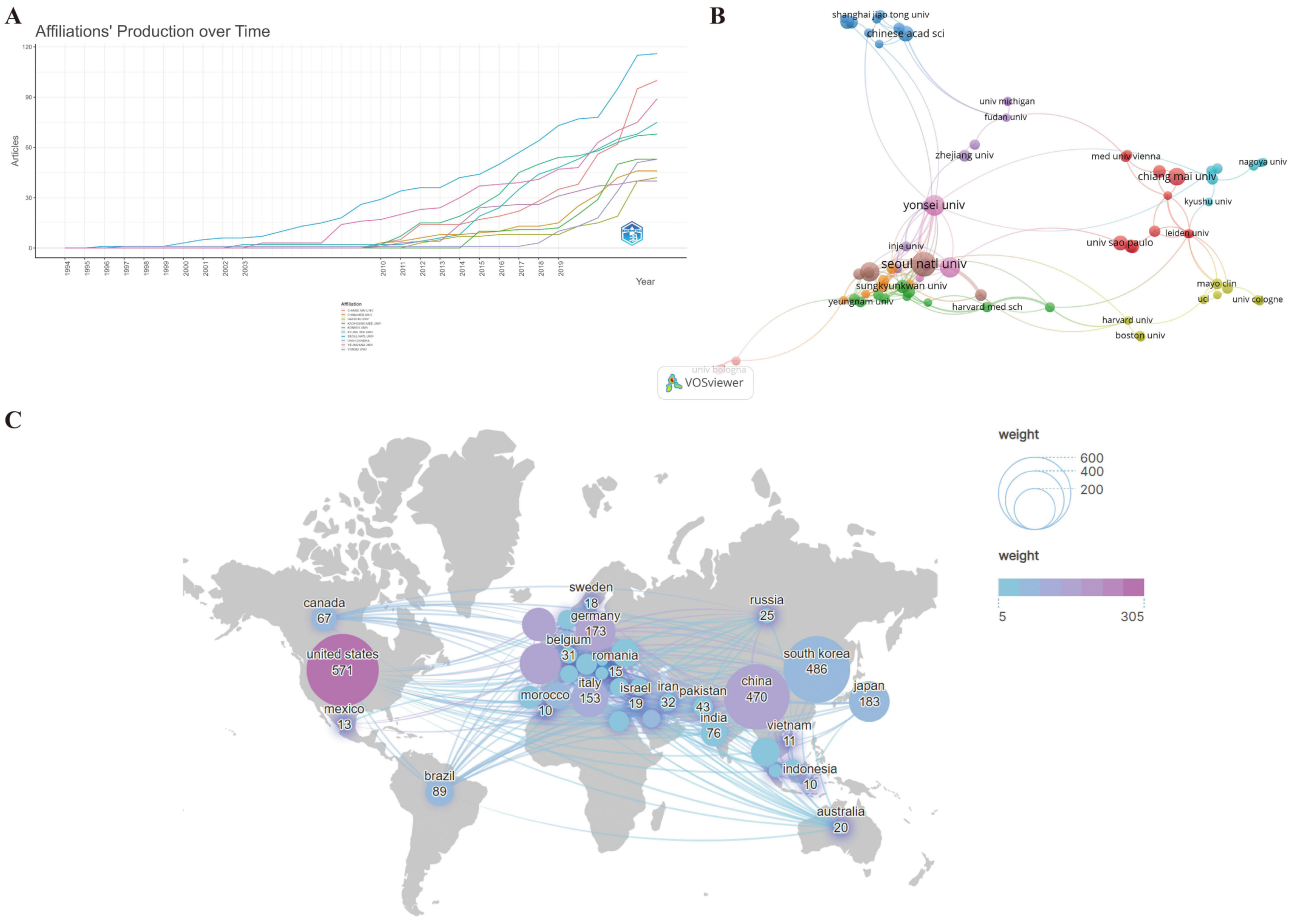

Figure 4 Core institutions, countries/regions and their cooperation. (**A**) Cumulative publication trends for the top 10 institutions. (**B**) Cluster analysis of inter-institutional collaboration. (**C**) Cluster analysis of international cooperation.

production over time of the institutions (Figure 4A), Seoul National University was the first to publish articles, and the number of articles increased rapidly from 78 in 2021 to 115 in 2023. Chiang Mai University started to publish articles rapidly from 62 in 2022 to 95 in 2023. Figure 4B describes the collaborative association between institutions, and the core issuing institutions are consistent with the above.

Based on the countries of the top 20 corresponding authors, Korea has the most publications (467), followed by USA (428), and China (417). These three are the core issuing countries in this field. In terms of countries' scientific production, China has the most (1,511), followed by South Korea (1,507) and USA (1,309). The core countries are well ahead of other countries when it comes to country production over time. Trend-wise, USA maintains the leading trend in terms of publications until 2021, and is overtaken by Korea after 2021, and by China in 2023. However, USA is also the most cited countries with 21,312 total citations, followed by Korea (8,260) and China (6,868). Figure 4C shows the volume of publications and the intensity of collaborations among countries.

Analysis of Keywords

After counting and merging the keywords, top 10 keywords include: gene-expression, skin, cellular senescence, cell, oxidative stress, antioxidants, in vitro, fibroblasts, mechanism, cancer. We performed clustering and trend analysis of authors keywords (Figure 5A–D). Current research in this field can be divided into 3 main categories: a. Mechanistic research: mechanisms of cellular senescence and apoptosis, research on biomarkers, cell biological processes, research on aging-related diseases, application of experimental animal models, and effects of stress and injury. These are important for understanding the aging process and developing anti-aging strategies; b. Applied research: skin anti-aging, research and development of skin care products, ingredient analysis, and product testing, which are important for the development of effective anti-aging products as well as for evaluating the safety and efficacy of the products; c. External factors: the response of skin cells to a variety of environmental factors including UV irradiation and oxidative stress, and how these

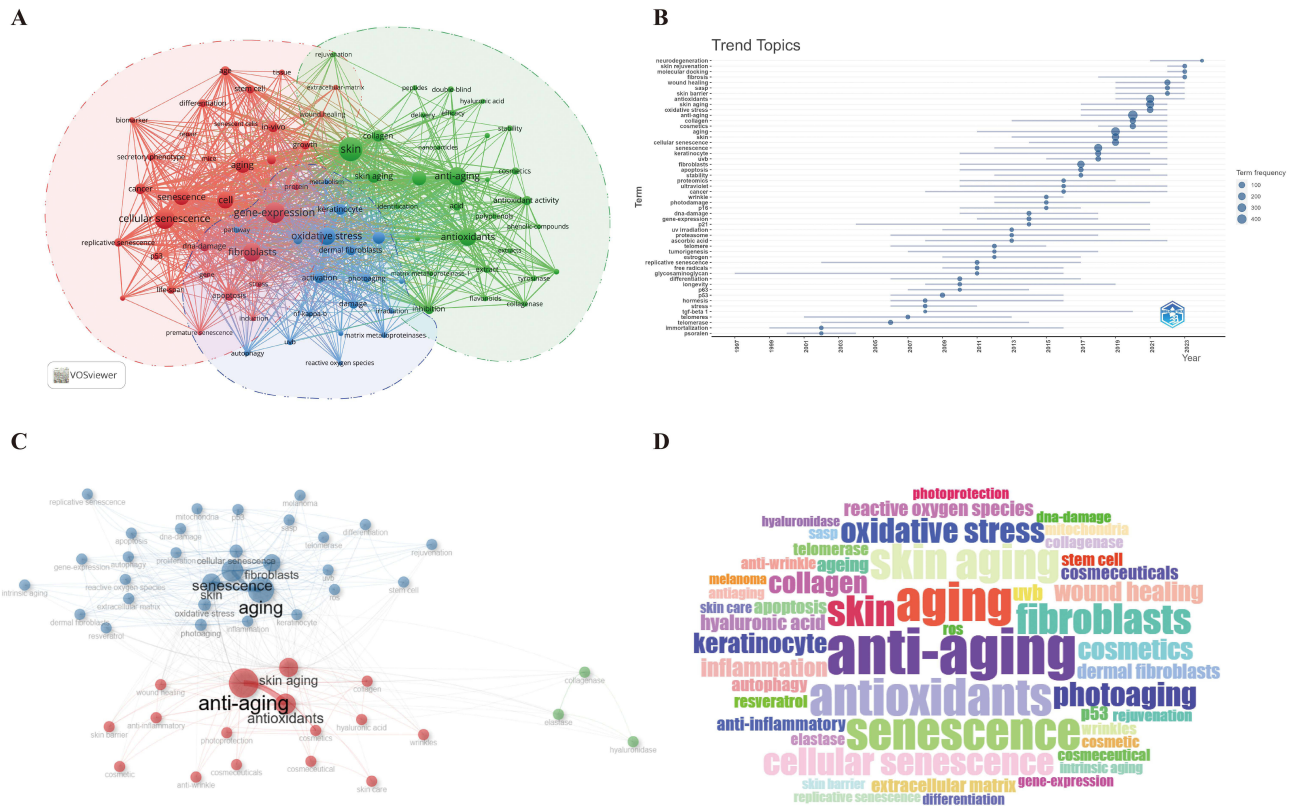

Figure 5 Core keyword clustering and trends analysis. (**A**) Cluster analysis of core keywords using VOSviewer. (**B**) Analysis of annual trend themes. (**C**) Cluster analysis of core keywords using R. (**D**) Word map analysis of core keywords.

factors contribute to skin aging and damage. Also, this section deals with the biomolecules and signaling pathways associated with skin aging and the use of natural compounds (eg, resveratrol) in anti-aging. Current research trends are focused on neurodegeneration, skin rejuvenation, molecular docking, fibrosis, wound healing, SASP, skin barrier, and antioxidants. The trend orientation of these studies is not only related to the aging of the population and the increasing incidence of related diseases, but also to the importance of skin appearance and the growing demand for anti-aging.

Analysis of Documents and References

We intensively read and analyzed the top 10 cited documents and references (Table 3 and Table 4). The number one overall cited document (5,831) is the study entitled "A biomarker that identifies senescent human cells in culture and in aging skin in vivo" by Dimri et al published in 1995 in Proceedings of the National Academy of Sciences of the United States of America.[31] This paper directly identified a gradual increase of beta-galactosidase with age in dermal fibroblasts and epidermal keratinocytes, which represents the accumulation of senescent cells. This literature was also the most cited reference of all the literature in this search. Secondly, the most cited document overall (3,987) was an original study by

Table 3 Top10 Global Cited Documents

Rank	Title	First Author	Year	Journal	Total Citations	DOI
1	A biomarker that identifies senescent human cells in culture and in aging skin in vivo	Dimri GP	1995	Proceedings of The National Academy of Sciences of The United States of America	5831	10.1073/pnas.92.20.9363
2	Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a	Serrano M	1997	Cell	3987	10.1016/S0092-8674(00)81,902–9
3	Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging	Krtolica A	2001	Proceedings of The National Academy of Sciences of The United States of America	1222	10.1073/pnas.211053698
4	Melanoma biology and new targeted therapy	Gray-Schopfer V	2007	Nature	1054	10.1038/nature05661
5	The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing	Jun JI	2010	Nature Cell Biology	682	10.1038/ncb2070
6	Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study	Justice JN	2019	Ebiomedicine	631	10.1016/j.ebiom.2018.12.052
7	Stress-activated cap'n'collar transcription factors in aging and human disease	Sykiotis GP	2010	Science Signaling	628	10.1126/scisignal.3112re3
8	Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease	Hickson LJ	2019	Ebiomedicine	627	10.1016/j.ebiom.2019.08.069
9	Augmented Wnt signaling in a mammalian model of accelerated aging	Liu HJ	2007	Science	597	10.1126/science.1143578
10	Microarray analysis of replicative senescence	Shelton DN	1999	Current Biology	558	10.1016/S0960-9822(99)80,420–5

Table 4 Top10 Local Cited References

Rank	Title	First Author	Year	Journal	Citations	DOI
1	A biomarker that identifies senescent human cells in culture and in aging skin in vivo	Dimri GP	1995	Proceedings of The National Academy of Sciences of The United States of America	325	10.1073/PNAS.92.20.9363
2	Mechanisms of photoaging and chronological skin aging	Fisher GJ	2002	Archives of dermatology	170	10.1001/ARCHDERM.138.11.1462
3	The hallmarks of aging	L Pez-Ot N C	2013	Cell	156	10.1016/J.CELL.2013.05.039
4	The serial cultivation of human diploid cell strains	Hayflick L	1961	Experimental cell research	154	10.1016/0014-4827(61)90,192–6
5	The senescence-associated secretory phenotype: the dark side of tumor suppression	Copp JP	2010	Annual Review of Pathology-Mechanisms of Disease	129	10.1146/ANNUREV-PATHOL-121808-102,144
6	Cellular senescence: when bad things happen to good cells	Campisi J	2007	Nature Reviews Molecular Cell Biology	117	10.1038/NRM2233
7	The limited in vitro lifetine of human diploid cell strains	Hayflick L	1965	Experimental cell research	116	10.1016/0014-4827(65)90,211–9
8	p16INK4A is a robust in vivo biomarker of cellular aging in human skin	Ressler S	2006	Aging Cell	115	10.1111/J.1474–9726.2006.00231.X
9	Pathophysiology of premature skin aging induced by ultraviolet light	Fisher GJ	1997	The New England Journal of Medicine	107	10.1056/NEJM199711133372003
10	Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor	Copp JP	2008	PLoS Biology	106	10.1371/JOURNAL.PBIO.0060301

Serrano et al published in *Cell* in 1997 entitled "Oncogenic ras provokes premature cell senescence associated with the accumulation of p53 and p16INK4a"[32] This study describes that the oncogene ras can cause cell cycle arrest, accompanied by the accumulation of p53 and p16 proteins, and that this cell cycle arrest is similar to the characteristics of cellular senescence. Krtolica A et al's original paper "Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging", published in *Proceedings of the National Academy of Sciences of the United States of America* in 2001, ranked 3rd in overall citations (1,222).[33] The article again linked cellular senescence and tumorigenesis, making the following three main points: a. senescent cells may suppress tumorigenesis at a young age but may promote tumorigenesis at an older age, reflecting antagonistic pleiotropy; b. senescent cells may create a suitable microenvironment for cells with oncogenic mutations; c. senescent cells with age-related mutations may synergistically promote tumorigenesis in old age.

In the reference analysis of all the literature, the 2nd cited literature is the review titled "Mechanisms of photoaging and chronological skin aging" by Fisher GJ et al published in *Archives of Dermatology*.[34] This article details the mechanisms of photoaging and skin aging and describes some of the molecular pathways by which UV exposure and the passage of time mediate skin damage. The 3rd cited reference is the review "The hallmarks of aging" by López-Otín etal in *Cell*.[35] This article reviews nine hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion,

and altered intercellular communication. These features reflect the major molecular and cellular changes during aging. Among them, section 7 states that senescent cell accumulation can affect tissue function and is an important hallmark of aging, and this article is based on this to provide a brief overview.

Discussion

Skin Aging

Skin covers the surface of the body, with a total adult skin area of about 1.5–2.0 m^2, accounting for about 16% of body weight, making it one of the largest organs in the human body. Skin aging is the most obvious feature of human aging and involves a complex biological process involving multiple cellular tissues. It can be divided into endogenous and exogenous aging.[36,37] Among them, endogenous aging is related to oxidative stress, programmed senescence caused by cellular damage, and cellular senescence. Exogenous aging, on the other hand, is the result of environmental factors such as ultraviolet (UV) radiation, air pollution, and tobacco smoke, which can lead to DNA damage and cellular dysfunction due to the production of reactive oxygen species (ROS).[38,39] Lifestyle factors such as diet and psychological stress are also closely associated with skin aging.[40,41] In addition, poor quality of sleep over a long period of time has been found to be associated with skin aging and poor skin barrier function.[42] The molecular mechanisms of skin aging have been summarized as follows: oxidative stress, DNA damage, telomere shortening, microRNA regulation, advanced glycation end product accumulation, genetic mutations, and chronic inflammation.[43]

Histologically, skin aging is characterized by epidermal and subcutaneous atrophy, flattening of the dermal-epidermal junction, degeneration of collagen and elastin fibers, and reduction of the cutaneous vascular system, with other hallmarks including wrinkles, roughness, loss of elasticity, and hyperpigmentation.[44] Biologically, the epidermis regenerates at a slower rate due to the reduced proliferative capacity of the keratinocyte-forming cell stem cells and depletion of the epidermal stem cell reservoirs, which leads to skin chronological thinning. Flattening of the epidermal/dermal interface makes the epidermis more vulnerable to shear forces and reduces nutrient flux between the epidermis and dermis, which in turn may negatively affect keratinocyte proliferation.[45] Alterations in melanocyte numbers and/or activity, in turn, lead to hypopigmented and hyperpigmented lesions in aging skin. Decreased collagen production and altered assembly of the elastin network result in loss of elasticity and lead to wrinkle formation in aging skin. To change the appearance and function of the skin, while positively influencing the health of the skin: This is also the focus of aesthetic medicine.

Mechanisms of Cellular Senescence

Cellular senescence refers to the gradual decline in the ability of normal cells to proliferate and differentiate in order to cope with DNA damage and to prevent the development of tumors. At this point, cells enter a state of permanent growth stagnation, and the process is accompanied by changes in cell morphology and a decline in normal physiological functions.[46] In addition, cellular senescence can lead to an increase in skin hyperpigmentation and inflammation, which further accelerates the process of skin aging. In aging skin, senescent cells accumulate and cause degradation of the extracellular matrix, further contributing to the aging process. The three main characteristics of senescent cells mainly include cell cycle arrest, secretion of senescence-associated secretory phenotype (SASP) and resistance to apoptosis. Senescent cells can exhibit three biomarkers: a. increased activity of the cell cycle arrest proteins $p21^{WAF1}$ and $p16^{INK4A}$; b. the lysosomal enzyme senescence-associated galactosidase (SA-β-gal); and c. decreased expression of the nuclear high-mobility group box-1 (HMGB1) and the nuclear fibrillar laminin B1, a structural component of the nuclear lamina.[47]

Among them, $p16^{INK4A}$ has been proposed as a biomarker of human aging[48] and it is now widely used by researchers to clinically assess the degree of aging with specific applications.[49] In one study, $p21^{WAF1}$ and $p16^{INK4A}$ were used to evaluate patients with primary sclerosing cholangitis in a correlation analysis between cholangiocyte senescence with disease severity and prognosis.[50] A meta-analysis found that positive expression of $p16^{INK4A}$ was associated with cancer-specific survival in patients with squamous cell carcinoma, indicating a prognostic value.[51] An ongoing prospective study is investigating the relationship between senescent cells and efficacy before and after laser treatment using $p16^{INK4A}$

immunohistochemical staining of skin biopsy sections from patients with hypertrophic scars.[52] In the case of SA-β-gal, previous studies have often used it as a criterion to evaluate the improvement of cellular senescence by drugs in in vitro experiments, while combining it with aging-related characteristics (eg skin elasticity, dermal density, wrinkles, skin hydration, etc). in clinical trials to evaluate anti-aging efficacy.[53,54]

In the skin, cell cycle arrest can directly lead to a significant reduction in the extracellular matrix content such as dermal collagen and elastin fibers, etc. It is manifested in signs of aging such as slower epidermal renewal, thinner thickness, increased trans-epidermal water loss, and impaired barrier function. In addition to stable cell growth arrest, senescent cells also secrete a series of inflammatory cytokines (IL-1, IL-6, IL-8), chemokines (GRO-α), growth factors (HGFs, IGFBPs), matrix proteases (MMP-1, MMP-3, MMP-9), and extracellular vesicles, collectively referred to as the SASP.[55] The accumulation of dysfunctional senescent cells decreases the repair and regeneration of tissues, leading to impaired tissue homeostasis, integrity, and function, which in turn has deleterious effects on the skin and contributes to a wide range of age-related diseases, such as seborrheic keratoses.[56–58] At the same time, the SASP from senescent cells elevates inflammatory signals that can cause tissue inflammation or a chronic state of inflammation, which can lead to an increased susceptibility to various cancers and an increased likelihood of distal metastases.[59,60] In addition, senescent cells have been found to have a bystander effect, being able to alter tissue homeostasis, and induce neighboring cell senescence both in vitro and in vivo, resulting in the accumulation of senescent cells.[61,62] SASP has been used in clinical trials to evaluate the anti-aging effects of drugs. Xiaofeng Tang et al[63] examined changes in SASP when studying autologous NK cell infusions in a healthy population. It was found that depleted T cells decreased after NK cell infusion, while SASP levels of IL-1α, IL-6, IL-8, IL-17, MIP-1α, MIP-1β and MMP1 also decreased. Meanwhile, through in vitro co-culture experiments, they found that NK cells could kill senescent CD4 T cells and avoid the bystander effect.

Resistance to Apoptosis

Except for cell cycle arrest and secretion of SASP, another important feature of senescent cells is resistance to apoptosis. Apoptosis is a programmed cell death pathway essential for tissue homeostasis, embryonic development, and immunity.[64,65] Normally, this process is precisely regulated by genes and maintains organismal homeostasis by removing senescent, damaged cells. In senescent cells, apoptosis acquires resistance, limiting the execution of the cell death program through endogenous and exogenous apoptotic pathways. In particular, the interaction between BH3-only proteins and the multi-structural domain B-cell lymphoma 2 protein family proteins (Bcl-2) family proteins modulates the endogenous apoptotic pathway initiated by mitochondria.[66,67] Under apoptotic conditions, the pro-apoptotic activators, BH3-only proteins (eg, Bid, Bim, Puma, etc), directly activate Bax and Bak, which can further promote the permeabilization of the outer mitochondrial membrane and the release of cytochrome C. Cytochrome C released from mitochondria can be assembled with apoptotic protease factor-1 (Apaf-1) to form apoptoticosome, which can activate the caspase cascade reaction to rapidly cleave the intracellular substrates (caspase-3, caspase-9, etc) and complete the process of apoptosis.[68–70]

In contrast, anti-apoptotic Bcl-2 homologous proteins (Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and A1) inhibit this process by binding to and chelating BH3-only proteins, directly inhibiting Bax and Bak, and preventing cytochrome C release and apoptoticosome formation.[66] Senescent cells, on the other hand, resist endogenous apoptosis by up-regulating the levels of these anti-apoptotic proteins and down-regulating pro-apoptotic activator levels to resist endogenous apoptosis. Besides, senescent cells also resist exogenous apoptosis by blocking the binding of death receptors to extracellular ligands. In particular, tumor necrosis factor (TNF) binding to TNF-α and Fas receptor binding to the ligand FasL form death-inducing signaling complex (DISC) and recruit and activate caspase activators (including caspase-8 and caspase-10), which cleave and activate effector caspases (such as caspase-3, caspase −6 and caspase-7), leading to degradation of intracellular components and induction of apoptosis.[64,71,72]

Apoptosis resistance plays an important role in the development of skin diseases. For example, psoriasis is a chronic inflammatory skin disease characterized by increased skin thickness and scaling. It has been shown that psoriasis patients can develop apoptosis resistance independent of the inflammatory component of the disease, which is manifested at the transcriptome level by upregulation of anti-apoptotic genes and downregulation of pro-apoptotic genes.[73] This may result in keratinocytes inability in the lesion area to undergo normal apoptosis, thus exacerbating the symptoms. A recent study

found that activation of the RAS/AKT pathway may perpetuate keratinocyte senescence in psoriasis via the P53/P21 axis.[74] Moreover, this study found that SA-β-gal positive staining was also significantly higher in lesional skin of psoriasis patients than in non-lesional areas.

Immune Clearance of Senescent Cells

Early studies have identified that senescent cells can be recognized and cleared by the immune system.[75,76] And this immune response plays an important role in the treatment of delayed aging. Depending on the pathophysiological context, senescence can not only induce an innate immune response using macrophages, neutrophils, and natural killer (NK) cells,[77] but also mediate the immune clearance of senescent cells through an adaptive immune response that relies on the interaction of antigen-specific CD4 T cells and monocytes/macrophages. Senescent cells acquire immunogenicity through the expression of stimulatory ligands such as MICA/B and ULBP2, which bind to expression of natural killer group 2 member D (NKG2D) and activate NK cell killing.[78,79] Recent studies have also found that cytotoxic CD4 T cells residing in the skin can be targeted to human cytomegalovirus glycoprotein B (HCMV-gB) in a human leukocyte antigen class II (HLA-II)-dependent manner to eliminate senescent cells.[80]

Moreover, senescent cells can achieve senescent cell clearance by secreting chemokines and cytokines that can recruit immune cells into tissues.[81] However, this secretory process may perpetuate the chronic inflammatory state of many age-related diseases.[59] Meanwhile, it has now been found that senescent cells can also achieve immune evasion. Senescent dermal fibroblasts expressing the nonclassical MHC molecule HLA-E, which interacts with the inhibitory receptor NKG2A expressed by NK and highly differentiated CD8 T cells to inhibit the immune clearance response against senescent cells.[82] Decreased immune function with age can also lead to incomplete clearance of senescent cells, and therefore therapies to improve apoptosis resistance and immune clearance of senescent cells have prompted researchers to dig deeper in their exploration.

Anti-Aging Strategies

Removal of senescent cells has become an important idea in today's anti-aging, and has led to the development of senotherapeutic strategies, including senolytic and senomorphic therapies.[83] Senolytic therapies are mainly used to clear senescent cells in the body, thereby reduce inflammation and oxidative stress and improve tissue function. Senomorphics therapies, on the other hand, focus on influencing the aging process by altering the phenotype (ie, the characteristics and functions of senescent cells) of senescent cells so that they no longer produce harmful signaling molecules, thereby reducing inflammation and tissue damage.

The three main targeting strategies, namely, senolysis, immune clearance, and SASP neutralization, have been developed.[23,84] Among them, immune-mediated senescent cell clearance mainly involves remodeling the immune system to re-immunosurveillance for regulatory purposes. It includes inhibition of senescent cell immune escape, employment of immunomodulators, or artificially increasing the number of immune effector cells, etc. Whereas SASP-neutralizing anti-aging strategies aim to combat senescence by interfering with senescent cell secretion, inhibiting SASP-related signaling cascade pathways, or inhibiting the secreted factor component alone.[85] This strategy does not really promote senescent cell clearance, but only mitigates, to some extent, the damage caused by senescent cells in tissues.

Compared to the other two anti-aging strategies, senolysis is currently a very promising approach for the treatment of senescent cells. It can selectively target and eliminate senescent cells by inhibiting the up-regulated anti-apoptotic pathway and reactivating the pro-apoptotic signaling pathway, thereby eliminating harmful SASP components in the environment for a long period of time, and thus achieving the desired anti-aging effect.[86] Moreover, since senolytic drugs are used to eliminate senescent cells at one time, they do not need to be used continuously, and can be given at intervals to maximize the efficacy of the treatment after the accumulation of senescent cells, which greatly improves patient compliance and drug safety.

Anti-Aging Drugs

Since the first antiaging agent in 2015, the number of antiaging drugs has shown a dramatic growth trend, and a variety of antiaging drug types such as kinase inhibitors, Bcl-2 family protein inhibitors, natural polyphenols, heat shock protein

inhibitors, BET family protein inhibitors, and P53 stabilizers have appeared.[87–89] The Src kinase inhibitor dasatinib and the quercetin (D+Q) were the earliest discovered anti-aging agents. It was found that D+Q treatment increased the expression of the pro-survival network in the transcriptome of senescent cells, selectively killed senescent cells in mice from different models of aging without killing proliferating or quiescent differentiated cells, ameliorated age-related disease progression and pathological changes, and prolonged the survival time of prematurely aging mice.[76] The first human trials of D+Q also demonstrated highly promising results, with the treatment reducing markers of aging in skin, blood, and adipose tissue[13] and improving physical function in a small sample of patients with idiopathic pulmonary fibrosis.[90,91]

Additionally, the anti-apoptotic inhibitors ABT-263 (navitoclax), piperlongumine, and ABT-737 have been characterized to target Bcl-2, Bcl-w, and Bcl-xL proteins to induce apoptosis and clear senescent cells, making them very promising anti-aging agents.[92–94] Current research is already attempting to apply chimeric antigen receptor (CAR)-T therapy to senolytic therapies. T cells specifically targeting senescent cell antigens are used to selectively remove senescent cells and exert anti-aging effects.[95,96] Nevertheless, there are still many difficulties and pain points in this field, mainly including drug activity, side effects, bioavailability and off-target effects, etc. It still needs more in-depth basic research and clinical trials to strive for further breakthroughs.

Limitation and Prospects

Although this paper explores cellular senescence and anti-aging strategies in the discussion section, there are some limitations. First, oxidative stress is not elaborated in this paper. Oxidative stress refers to an imbalance between intracellular ROS production and antioxidant defense systems, leading to cellular damage and dysfunction. Oxidative stress plays a key role in the aging process and is one of the main factors leading to skin aging. An in-depth understanding of the mechanisms of oxidative stress and intervention strategies is equally important for the development of effective anti-aging therapies. Secondly, some details in this paper have not been fully paid attention to, resulting in an incomplete discussion. For example, this paper mainly focuses on the relationship between cellular senescence and skin aging, but the discussion of other biological processes related to aging (eg, telomere shortening, mitochondrial dysfunction, etc). is limited. In addition, the advantages, disadvantages, and scope of application of different anti-aging strategies are not analyzed in depth in this paper, which may lead readers to have a less-than-comprehensive understanding of certain anti-aging therapies. Finally, this paper aims to provide researchers with a rough overview of cellular senescence and anti-aging strategies rather than an exhaustive overview.

As a result, this paper may fail to provide sufficient information on some specific research methods and cases. This may result in the reader needing to further consult other literature for more detailed information when delving into related topics. Nonetheless, this paper still provides a valuable reference for researchers to help them better understand the current state of research and future trends in this field. In future studies, we will continue to focus on key factors such as oxidative stress and endeavor to improve the comprehensiveness and depth of the exposition, with a view to providing more comprehensive theoretical support and practical guidance for dermatological aesthetics and anti-aging research.

Conclusion

Through bibliometric analysis, this study reveals that this field has shown a significant upward trend in research in recent years. Related research hotspots focus on oxidative stress, fibroblasts, and SASP. The literature review provided insights into the mechanisms of skin aging, cellular senescence processes, senescent cell removal strategies, and research advances in anti-aging drugs. These studies show that a wealth of research results have been achieved in this field. Cellular senescence-related indicators provide new biomarkers for the diagnosis of skin diseases and also play a key role in the prognostic assessment of diseases. Anti-aging strategies targeting cellular senescence include removing senescent cells or attenuating the effects of SASP factors to prevent or delay aging, which can be achieved through senolytic and senomorphic therapies. Particularly, senolytic therapy, as a novel anti-aging strategy, shows great potential for application and provides new ideas and therapeutic means to slow down the aging process.

Data Sharing Statement

The datasets generated and analyzed during the current study are available upon request from the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

References

1. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell*. 2023;186(2):243–278.
2. Lemaitre JM. Looking for the philosopher's stone: emerging approaches to target the hallmarks of aging in the skin. *JEADV*. 2024;38(4):5–14. doi:10.1111/jdv.19820
3. Tsitsipatis D, Martindale JL, Ubaida-Mohien C, et al. Proteomes of primary skin fibroblasts from healthy individuals reveal altered cell responses across the life span. *Aging Cell*. 2022;21(5):e13609. doi:10.1111/acel.13609
4. Bellei B, Picardo M. Premature cell senescence in human skin: dual face in chronic acquired pigmentary disorders. *Ageing Res Rev*. 2020;57:100981. doi:10.1016/j.arr.2019.100981
5. Kaur A, Ecker BL, Douglass SM, et al. Remodeling of the Collagen Matrix in Aging Skin Promotes Melanoma Metastasis and Affects Immune Cell Motility. *Cancer Discovery*. 2019;9(1):64–81. doi:10.1158/2159-8290.CD-18-0193
6. Hahnel E, Lichterfeld A, Blume-Peytavi U, Kottner J. The epidemiology of skin conditions in the aged: a systematic review. *J Tissue Viab*. 2017;26(1):20–28. doi:10.1016/j.jtv.2016.04.001
7. Childs BG, Gluscevic M, Baker DJ, et al. Senescent cells: an emerging target for diseases of ageing. *Nat Rev Drug Discov*. 2017;16(10):718–735. doi:10.1038/nrd.2017.116
8. Borghesan M, Hoogaars WMH, Varela-Eirin M, Talma N, Demaria M. A Senescence-Centric View of Aging: implications for Longevity and Disease. *Trends Cell Biol*. 2020;30(10):777–791. doi:10.1016/j.tcb.2020.07.002
9. Dańczak-Pazdrowska A, Gornowicz-Porowska J, Polańska A, et al. Cellular senescence in skin-related research: targeted signaling pathways and naturally occurring therapeutic agents. *Aging Cell*. 2023;22(6):e13845. doi:10.1111/acel.13845
10. Shetty AK, Kodali M, Upadhya R, Madhu LN. Emerging Anti-Aging Strategies - Scientific Basis and Efficacy. *Aging Dis*. 2018;9(6):1165–1184. doi:10.14336/AD.2018.1026
11. Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. *Dermato Endocrinol*. 2012;4(3):308–319. doi:10.4161/derm.22804
12. Robinson DM, Aasi SZ. Cosmetic concerns and management strategies to combat aging. *Maturitas*. 2011;70(3):256–260. doi:10.1016/j.maturitas.2011.07.020
13. Hickson LJ, Langhi Prata LGP, Bobart SA, et al. Senolytics decrease senescent cells in humans: preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. *EBioMed*. 2019;47:446–456. doi:10.1016/j.ebiom.2019.08.069
14. Bogdanowicz P, Bensadoun P, Noizet M, et al. Senomorphic activity of a combination of niacinamide and hyaluronic acid: correlation with clinical improvement of skin aging. *Sci Rep*. 2024;14(1):16321. doi:10.1038/s41598-024-66624-7
15. Ninkov A, Frank JR, Maggio LA. Bibliometrics: methods for studying academic publishing. *Perspect Med Educ*. 2022;11(3):173–176. doi:10.1007/S40037-021-00695-4
16. Kokol P, Vošner H B. Historical, descriptive and exploratory analysis of application of bibliometrics in nursing research. *Nursing Outlook*. 2019;67(6):680–695. doi:10.1016/j.outlook.2019.04.009
17. Sun PH, Yan WT, Tian RF, Sun Y, Wu Y. The landscape of photoaging: from bench to bedside in a bibliometric analysis. *Front Public Health*. 2022;10:972766. doi:10.3389/fpubh.2022.972766
18. Li C, Liu Z, Shi R. A comprehensive overview of cellular senescence from 1990 to 2021: a machine learning-based bibliometric analysis. *Front Med*. 2023;10:1072359. doi:10.3389/fmed.2023.1072359
19. Wang S, Yang J, Xiang R, et al. Research and publication trends on knee osteoarthritis and cellular senescence: a bibliometric analysis. *Front Physiol*. 2023;14:1269338. doi:10.3389/fphys.2023.1269338
20. Ding X, Huang J, Zhou R, et al. Bibliometric study and visualization of cellular senescence associated with osteoarthritis from 2009 to 2023. *Medicine*. 2024;103(17):e37611. doi:10.1097/MD.0000000000037611

21. Yue Z, Nie L, Zhao P, Ji N, Liao G, Wang Q. Senescence-associated secretory phenotype and its impact on oral immune homeostasis. *Front Immunol*. 2022;13:1019313. doi:10.3389/fimmu.2022.1019313
22. Wyles SP, Carruthers JD, Dashti P, et al. Cellular Senescence in Human Skin Aging: leveraging Senotherapeutics. *Gerontology*. 2024;70(1):7–14. doi:10.1159/000534756
23. Thompson EL, Pitcher LE, Niedernhofer LJ, Robbins PD. Targeting Cellular Senescence with Senotherapeutics: development of New Approaches for Skin Care. *Plastic Reconstruct Surg*. 2022;150:12s–19s. doi:10.1097/PRS.0000000000009668
24. Pranckutė R. Web of Science (WoS) and Scopus: the Titans of Bibliographic Information in Today's Academic World. *Publications*. 2021;9(1):12. doi:10.3390/publications9010012
25. Birkle C, Pendlebury DA, Schnell J, Adams J. Web of Science as a data source for research on scientific and scholarly activity. *Quantit Sci Stud*. 2020;1(1):363–376. doi:10.1162/qss_a_00018
26. Aria M, Cuccurullo C. bibliometrix: an R-tool for comprehensive science mapping analysis. *J Inform*. 2017;11(4):959–975. doi:10.1016/j.joi.2017.08.007
27. van Eck NJ, Waltman L. Software survey: vOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. doi:10.1007/s11192-009-0146-3
28. Waltman L, van Eck NJ, Noyons ECM. A unified approach to mapping and clustering of bibliometric networks. *J Inform*. 2010;4(4):629–635. doi:10.1016/j.joi.2010.07.002
29. Hassan-Montero Y, De-Moya-Anegón F, Guerrero-Bote VP. SCImago Graphica: a new tool for exploring and visually communicating data. *El Profesional de la información*. 2022. doi:10.3145/epi.2022.sep.02
30. Hassan-Montero Y, Guerrero-Bote VP, De-Moya-Anegón F. Graphical interface of the *SCImago Journal and Country Rank*: an interactive approach to accessing bibliometric information. *Prof Inform*. 2014;23(3):272–278. doi:10.3145/epi.2014.may.07
31. Dimri GP, Lee X, Basile G, et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proc Natl Acad Sci USA*. 1995;92(20):9363–9367. doi:10.1073/pnas.92.20.9363
32. Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. *Cell*. 1997;88(5):593–602. doi:10.1016/S0092-8674(00)81902-9
33. Krtolica A, Parrinello S, Lockett S, Desprez PY, Campisi J. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. *Proc Natl Acad Sci USA*. 2001;98(21):12072–12077. doi:10.1073/pnas.211053698
34. Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol*. 2002;138(11):1462–1470. doi:10.1001/archderm.138.11.1462
35. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–1217. doi:10.1016/j.cell.2013.05.039
36. Shin SH, Lee YH, Rho NK, Park KY. Skin aging from mechanisms to interventions: focusing on dermal aging. *Front Physiol*. 2023;14:1195272. doi:10.3389/fphys.2023.1195272
37. Franco AC, Aveleira C, Cavadas C. Skin senescence: mechanisms and impact on whole-body aging. *Trends Mol Med*. 2022;28(2):97–109. doi:10.1016/j.molmed.2021.12.003
38. Papaccio F, Da A, Caputo S, Bellei B. Focus on the Contribution of Oxidative Stress in Skin Aging. *Antioxidants*. 2022;11(6). doi:10.3390/antiox11061121
39. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Res Rev*. 2020;59:101036. doi:10.1016/j.arr.2020.101036
40. Cao C, Xiao Z, Wu Y, Ge C. Diet and Skin Aging-From the Perspective of Food Nutrition. *Nutrients*. 2020;12(3):870. doi:10.3390/nu12030870
41. Lee CM, Watson REB, Kleyn CE. The impact of perceived stress on skin ageing. *JEADV*. 2020;34(1):54–58. doi:10.1111/jdv.15865
42. Oyetakin-White P, Suggs A, Koo B, et al. Does poor sleep quality affect skin ageing? *Clin Exp Dermatol*. 2015;40(1):17–22. doi:10.1111/ced.12455
43. Zhang S, Duan E. Fighting against Skin Aging: the Way from Bench to Bedside. *Cell Transplant*. 2018;27(5):729–738. doi:10.1177/0963689717725755
44. Bonta M, Daina L, Muțiu G. The process of ageing reflected by histological changes in the skin. *Rom J Morphol Embryol*. 2013;54(3 Suppl):797–804.
45. Farage MA, Miller KW, Elsner P, Maibach HI. Characteristics of the Aging Skin. *Adv Wound Care*. 2013;2(1):5–10. doi:10.1089/wound.2011.0356
46. Sharpless NE, Sherr CJ. Forging a signature of in vivo senescence. *Nat Rev Cancer*. 2015;15(7):397–408. doi:10.1038/nrc3960
47. Ho CY, Dreesen O. Faces of cellular senescence in skin aging. *Mechanisms Age Develop*. 2021;198:111525. doi:10.1016/j.mad.2021.111525
48. Liu Y, Sanoff HK, Cho H, et al. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell*. 2009;8(4):439–448. doi:10.1111/j.1474-9726.2009.00489.x
49. Carroll JE, Olmstead R, Cole SW, Breen EC, Arevalo JM, Irwin MR. Remission of insomnia in older adults treated with cognitive behavioral therapy for insomnia (CBT-I) reduces p16(INK4a) gene expression in peripheral blood: secondary outcome analysis from a randomized clinical trial. *GeroScience*. 2023;45(4):2325–2335. doi:10.1007/s11357-023-00741-5
50. Cazzagon N, Sarcognato S, Floreani A, et al. Cholangiocyte senescence in primary sclerosing cholangitis is associated with disease severity and prognosis. *JHEP Rep*. 2021;3(3):100286. doi:10.1016/j.jhepr.2021.100286
51. Zhang J, Zhang H, Xiu Y, Cheng H, Gu M, Song N. Prognostic Significance of P16(INK4a) Expression in Penile Squamous Cell Carcinoma: a Meta-Analysis with Trial Sequential Analysis. *Biomed Res Int*. 2018;2018:8345893. doi:10.1155/2018/8345893
52. Chen YY, Patel KM, Imran R, et al. SMOOTH protocol: a pilot randomised prospective intra-patient single-blinded observational study for examining the mechanistic basis of ablative fractional carbon dioxide laser therapy in treating hypertrophic scarring. *PLoS One*. 2023;18(9):e0285230. doi:10.1371/journal.pone.0285230
53. Choi S, Youn J, Kim K, et al. Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. *IntJ Mol Med*. 2016;38(2):627–634. doi:10.3892/ijmm.2016.2626
54. Lee SG, Ham S, Lee J, et al. Evaluation of the anti-aging effects of Zinc-α2-glycoprotein peptide in clinical and in vitro study. *Skin Res Technol*. 2024;30(3):e13609. doi:10.1111/srt.13609

55. Fitsiou E, Pulido T, Campisi J, Alimirah F, Demaria M. Cellular Senescence and the Senescence-Associated Secretory Phenotype as Drivers of Skin Photoaging. *J Invest Dermatol*. 2021;141(4):1119–1126. doi:10.1016/j.jid.2020.09.031
56. Wlaschek M, Maity P, Makrantonaki E, Scharffetter-Kochanek K. Connective Tissue and Fibroblast Senescence in Skin Aging. *J Invest Dermatol*. 2021;141(4s):985–992. doi:10.1016/j.jid.2020.11.010
57. Li Y, Wang Y, Zhang W, et al. Overexpression of Amyloid Precursor Protein Promotes the Onset of Seborrhoeic Keratosis and is Related to Skin Ageing. *Acta Dermato Venereol*. 2018;98(6):594–600. doi:10.2340/00015555-2911
58. Nakamura S, Nishioka K. Enhanced expression of p16 in seborrhoeic keratosis; a lesion of accumulated senescent epidermal cells in G1 arrest. *Br J Dermatol*. 2003;149(3):560–565. doi:10.1046/j.1365-2133.2003.05589.x
59. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A*. 2014;69(1):S4–9. doi:10.1093/gerona/glu057
60. Fulop T, Witkowski JM, Olivieri F, Larbi A. The integration of inflammaging in age-related diseases. *Semin Immunopathol*. 2018;40:17–35. doi:10.1016/j.smim.2018.09.003
61. da Silva PFL, Ogrodnik M, Kucheryavenko O, et al. The bystander effect contributes to the accumulation of senescent cells in vivo. *Aging Cell*. 2019;18(1):e12848. doi:10.1111/acel.12848
62. Hodny Z, Hubackova S, Bartek J. Cytokine-induced 'bystander' senescence in DDR and immuno-surveillance. *Oncotarget*. 2013;4(10):1552–1553. doi:10.18632/oncotarget.1487
63. Tang X, Deng B, Zang A, et al. Characterization of age-related immune features after autologous NK cell infusion: protocol for an open-label and randomized controlled trial. *Front Immunol*. 2022;13:940577. doi:10.3389/fimmu.2022.940577
64. Park W, Wei S, Kim BS, et al. Diversity and complexity of cell death: a historical review. *Exp Mol Med*. 2023;55(8):1573–1594. doi:10.1038/s12276-023-01078-x
65. Bedoui S, Herold MJ, Strasser A. Emerging connectivity of programmed cell death pathways and its physiological implications. *Nat Rev Mol Cell Biol*. 2020;21(11):678–695. doi:10.1038/s41580-020-0270-8
66. King LE, Rodriguez-Enriquez R, Pedley R, et al. Apoptotic priming is defined by the dynamic exchange of Bcl-2 proteins between mitochondria and cytosol. *Cell Death Differ*. 2022;29(11):2262–2274. doi:10.1038/s41418-022-01013-z
67. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. *Nat Rev Mol Cell Biol*. 2014;15(1):49–63. doi:10.1038/nrm3722
68. Peña-Blanco A, Bax G-SAJ. Bak and beyond - mitochondrial performance in apoptosis. *FEBS J*. 2018;285(3):416–431. doi:10.1111/febs.14186
69. Cao K, Riley JS, Heilig R, et al. Mitochondrial dynamics regulate genome stability via control of caspase-dependent DNA damage. *Dev Cell*. 2022;57(10):1211–1225.e1216. doi:10.1016/j.devcel.2022.03.019
70. Ow YP, Green DR, Hao Z, Mak TW. Cytochrome c: functions beyond respiration. *Nat Rev Mol Cell Biol*. 2008;9(7):532–542. doi:10.1038/nrm2434
71. Riedl SJ, Shi Y. Molecular mechanisms of caspase regulation during apoptosis. *Nat Rev Mol Cell Biol*. 2004;5(11):897–907. doi:10.1038/nrm1496
72. Ashkenazi A. Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nat Rev Cancer*. 2002;2(6):420–430. doi:10.1038/nrc821
73. Eding CB, Enerbäck C. Involved and Uninvolved Psoriatic Keratinocytes Display a Resistance to Apoptosis that may Contribute to Epidermal Thickness. *Acta Dermato Venereol*. 2017;97(7):788–796. doi:10.2340/00015555-2656
74. Mercurio L, Bailey J, Glick AB, et al. RAS-activated PI3K/AKT signaling sustains cellular senescence via P53/P21 axis in experimental models of psoriasis. *J Dermatological Sci*. 2024;115(1):21–32. doi:10.1016/j.jdermsci.2024.03.002
75. Hoenicke L, Zender L. Immune surveillance of senescent cells--biological significance in cancer- and non-cancer pathologies. *Carcinogenesis*. 2012;33(6):1123–1126. doi:10.1093/carcin/bgs124
76. Zhu Y, Tchkonia T, Pirtskhalava T, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*. 2015;14(4):644–658. doi:10.1111/acel.12344
77. Xue W, Zender L, Miething C, et al. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature*. 2007;445:7128):656–660. doi:10.1038/nature05529
78. Sagiv A, Burton DG, Moshayev Z, et al. NKG2D ligands mediate immunosurveillance of senescent cells. *Aging*. 2016;8(2):328–344. doi:10.18632/aging.100897
79. Martyshkina YS, Tereshchenko VP, Bogdanova DA, Rybtsov SA. Reliable Hallmarks and Biomarkers of Senescent Lymphocytes. *Int J Mol Sci*. 2023;24(21):15653. doi:10.3390/ijms242115653
80. Hasegawa T, Oka T, Son HG, et al. Cytotoxic CD4(+) T cells eliminate senescent cells by targeting cytomegalovirus antigen. *Cell*. 2023;186(7):1417–1431.e1420. doi:10.1016/j.cell.2023.02.033
81. Iannello A, Thompson TW, Ardolino M, Lowe SW, Raulet DH. p53-dependent chemokine production by senescent tumor cells supports NKG2D-dependent tumor elimination by natural killer cells. *J Exp Med*. 2013;210(10):2057–2069. doi:10.1084/jem.20130783
82. Pereira BI, Devine OP, Vukmanovic-Stejic M, et al. Senescent cells evade immune clearance via HLA-E-mediated NK and CD8(+) T cell inhibition. *Nat Commun*. 2019;10(1):2387. doi:10.1038/s41467-019-10335-5
83. Di Micco R, Krizhanovsky V, Baker D, d'Adda Di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021;22(2):75–95. doi:10.1038/s41580-020-00314-w
84. Robbins PD, Jurk D, Khosla S, et al. Senolytic Drugs: reducing Senescent Cell Viability to Extend Health Span. *Annu Rev Pharmacol Toxicol*. 2021;61(1):779–803. doi:10.1146/annurev-pharmtox-050120-105018
85. Shrestha N, Chaturvedi P, Zhu X, et al. Immunotherapeutic approach to reduce senescent cells and alleviate senescence-associated secretory phenotype in mice. *Aging Cell*. 2023;22(5):e13806. doi:10.1111/acel.13806
86. Martin N, Popgeorgiev N, Ichim G, Bernard D. BCL-2 proteins in senescence: beyond a simple target for senolysis? *Nat Rev Mol Cell Biol*. 2023;24(8):517–518. doi:10.1038/s41580-023-00594-y
87. Power H, Valtchev P, Dehghani F, Schindeler A. Strategies for senolytic drug discovery. *Aging Cell*. 2023;22(10):e13948. doi:10.1111/acel.13948
88. Wakita M, Takahashi A, Sano O, et al. A BET family protein degrader provokes senolysis by targeting NHEJ and autophagy in senescent cells. *Nat Commun*. 2020;11(1):1935. doi:10.1038/s41467-020-15719-6

89. Zhang L, Pitcher LE, Prahalad V, Niedernhofer LJ, Robbins PD. Recent advances in the discovery of senolytics. *Mechanisms Age Develop*. 2021;200:111587. doi:10.1016/j.mad.2021.111587
90. Justice JN, Nambiar AM, Tchkonia T, et al. Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study. *EBioMed*. 2019;40:554–563. doi:10.1016/j.ebiom.2018.12.052
91. Nambiar A, Kellogg D 3rd, Justice J, et al. Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: results of a Phase I, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and tolerability. *EBioMed*. 2023;90:104481. doi:10.1016/j.ebiom.2023.104481
92. Chang J, Wang Y, Shao L, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. *Nature Med*. 2016;22(1):78–83. doi:10.1038/nm.4010
93. Zhu Y, Tchkonia T, Fuhrmann-Stroissnigg H, et al. Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. *Aging Cell*. 2016;15(3):428–435. doi:10.1111/acel.12445
94. Ritschka B, Knauer-Meyer T, Gonçalves DS, et al. The senotherapeutic drug ABT-737 disrupts aberrant p21 expression to restore liver regeneration in adult mice. *Genes Dev*. 2020;34(7–8):489–494. doi:10.1101/gad.332643.119
95. Amor C, Feucht J, Leibold J, et al. Senolytic CAR T cells reverse senescence-associated pathologies. *Nature*. 2020;583(7814):127–132. doi:10.1038/s41586-020-2403-9
96. Yang D, Sun B, Li S, et al. NKG2D-CAR T cells eliminate senescent cells in aged mice and nonhuman primates. *Sci Trans Med*. 2023;15(709):eadd1951. doi:10.1126/scitranslmed.add1951

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