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CELLULAR SENESCENCE: MOLECULAR MECHANISMS AND SENOLYTIC AND SENOMORPHIC STRATEGIES

Nargiza Hamzayeva[1*], Anvar Normatov[2], Gulnoza Jakhangirova[3], Madina Khamidova[4], Mohira Khamidova[5], Dilafruz Zaynutdinova[6], Zilola Rabimova[7], Rakhmonova Dildor[8]

[1,6] Tashkent State Medical University, Tashkent, Uzbekistan;
[2,3,4,5]Tashkent Institute of Chemical and Technology, Tashkent, Uzbekistan;
[7,8]Turon University, Karshi, Uzbekistan;
*Corresponding Author: Nargiza Hamzayeva, Email: nargiza@tashmeduni.uz

ABSTRACT
Cellular senescence is an irreversible cell cycle arrest associated with chronic inflammation and age-related diseases. Senescent cells develop a senescence-associated secretory phenotype (SASP), largely regulated by NF-κB signaling, which promotes tissue dysfunction and inflammaging. Key molecular pathways involved in senescence include p53/p21, p16INK4a/Rb, and SIRT1-mediated regulation. Recent therapeutic strategies focus on senolytics, which selectively eliminate senescent cells, and senomorphics, which suppress their harmful phenotype without inducing cell death. Natural flavonoids such as quercetin and rutin have shown promising senomorphic and context-dependent senolytic effects through antioxidant activity, NF-κB inhibition, and SIRT1 activation. This review summarizes the molecular mechanisms of cellular senescence and highlights current senotherapeutic approaches with emphasis on SIRT1 and flavonoid-based interventions as potential anti-aging strategies.

KEYWORDS: cellular senescence, senolytics, senomorphics, SIRT1, NF-κB, SASP, flavonoids, quercetin, aging, inflammaging

INTRODUCTION

Cellular aging is a major biological process involved in the development of many chronic and degenerative diseases. One of the main hallmarks of aging is cellular senescence, a state of irreversible cell cycle arrest that occurs in response to various internal and external stress factors, including oxidative damage and DNA instability (1,2). Initially, senescence serves as a protective mechanism against malignant transformation; however, over time, the accumulation of senescent cells disrupts tissue function and promotes chronic inflammation (3). Senescent cells are characterized not only by growth arrest but also by the development of a pro-inflammatory phenotype known as the senescence-associated secretory phenotype (SASP). This phenotype involves the secretion of cytokines, chemokines, and proteases that disturb tissue homeostasis and contribute to the progression of age-related diseases. A central role in this process is played by the NF-κB signaling pathway, which regulates the expression of inflammatory genes and reinforces the senescent state (4, 5).

At the molecular level, cellular senescence is regulated by tumor suppressor pathways, particularly the p53 pathway and cyclin-dependent kinase inhibitors such as p16INK4a. These pathways induce permanent growth arrest in response to cellular stress (3,4,5). However, persistent activation of these mechanisms leads to the accumulation of dysfunctional cells, thereby accelerating aging and disease progression. In recent years, therapeutic strategies targeting senescent cells have gained significant attention. Two major approaches have emerged: senolytics, which selectively eliminate senescent cells, and senomorphics, which modulate the senescent phenotype without inducing cell death. These strategies offer promising opportunities to alleviate age-related pathologies and improve healthspan (6, 7, 8).

Among the molecular regulators of senescence, sirtuins, particularly SIRT1, have attracted considerable interest due to their role in controlling cellular stress responses, inflammation, and metabolic homeostasis. SIRT1 exerts its effects through the deacetylation of key transcription factors, including p53 and NF-κB, thereby influencing both senescence and inflammatory signaling pathways (9, 10). Natural bioactive compounds, especially flavonoids such as quercetin, are increasingly recognized for their ability to modulate senescence-related pathways. These compounds possess antioxidant, anti-inflammatory, and SIRT1-regulating properties, suggesting a dual role as senomorphic agents and, under certain conditions, as senolytic agents (11,12,13,14).

This review aims to provide a comprehensive overview of senolytics and senomorphics, with particular emphasis on their molecular mechanisms and the emerging role of SIRT1 modulation. Special attention is given to flavonoid-based compounds as potential therapeutic agents targeting cellular senescence in a stress-dependent manner.

Molecular Mechanisms of Cellular Senescence

Cellular senescence is a complex and highly regulated biological process controlled by multiple interconnected molecular pathways. It is primarily initiated in response to various internal and external stress factors, including DNA damage, oxidative stress, and telomere shortening. These stress signals activate key regulatory networks that induce stable and irreversible cell cycle arrest (15,16).

One of the central pathways governing senescence is the p53 pathway. In response to DNA damage or cellular stress, p53 becomes activated and transcriptionally induces downstream targets such as p21, which inhibits cyclin-dependent kinases and prevents cell cycle progression. As a result, a strong growth arrest is established, preventing the proliferation of damaged cells. Although initially protective, persistent activation of the p53–p21 axis can lead to long-term cellular dysfunction (17,18). In parallel, the p16INK4a pathway plays a crucial role in maintaining senescence. p16INK4a inhibits CDK4/6 activity, leading to activation of the retinoblastoma (Rb) protein and permanent withdrawal from the cell cycle. The p16INK4a pathway is commonly associated with irreversible senescence and is considered a hallmark of aging tissues (19, 20). A characteristic feature of senescent cells is the development of the senescence-associated secretory phenotype (SASP). This phenotype involves the secretion of numerous pro-inflammatory cytokines (such as IL-6 and IL-8), growth factors, and matrix-remodeling enzymes. SASP reinforces the senescent state through autocrine signaling and induces paracrine senescence in neighboring cells, thereby exacerbating tissue dysfunction (21, 22). Regulation of SASP is closely linked to activation of the NF-κB signaling pathway. Persistent NF-κB activation drives chronic inflammatory signaling and contributes to the pathogenesis of age-related diseases (23). Importantly, epigenetic and metabolic regulators also contribute to the control of senescence. Among them, sirtuins, particularly SIRT1, play a significant role. As mentioned above, SIRT1 modulates senescence by deacetylating key transcription factors such as p53 and NF-κB, thereby attenuating both cell cycle arrest and inflammatory responses. Reduced SIRT1 activity has been associated with enhanced senescence and age-related dysfunction (24, 25, 26).

Overall, cellular senescence arises from the dynamic interplay between cell cycle regulators, inflammatory signaling pathways, and metabolic control mechanisms. Understanding these molecular processes provide an important foundation for the development of targeted therapeutic strategies such as senolytics and senomorphics (15, 16).

Senolytics: Mechanisms and Major Compounds

Senolytics are a class of therapeutic agents designed to selectively eliminate senescent cells by targeting their survival mechanisms (27, 28). One of the primary targets of senolytic therapy is the family of anti-apoptotic proteins belonging to the BCL-2 family, which are often overexpressed in senescent cells. One of the best-known senolytic compounds is navitoclax, which inhibits members of the BCL-2 family and effectively clears senescent cells in various experimental models (29, 30). However, its clinical application is limited due to dose-dependent toxicity. Another widely studied senolytic strategy is the combination of dasatinib and quercetin. This combination has been shown to effectively reduce senescent cell burden in both in vitro and in vivo studies and has also been evaluated in clinical trials (31, 32, 33). The combination has attracted attention because of its relatively broad activity across different types of senescent cells. Mechanistically, senolytics function by disrupting key survival pathways in senescent cells. This includes inhibition of anti-apoptotic signaling pathways, particularly those involving the BCL-2 family (34, 35, 36). Since senescent cells rely heavily on these pathways for survival, their inhibition selectively induces cell death with relatively limited effects on normal cells. Despite their promising therapeutic potential, senolytics face several challenges. Off-target effects and systemic toxicity remain major concerns, especially for agents targeting broadly expressed survival proteins. In addition, the heterogeneity of senescent cells across different tissues complicates the identification of universal senolytic targets (37, 38, 39).

Overall, senolytics provide a powerful strategy for directly reducing the burden of senescent cells. However, further research is required to optimize their safety profile and better understand their long-term effects in clinical settings.

Senomorphics: Modulating Senescence Without Eliminating Cells

Unlike senolytics, senomorphics represent an alternative therapeutic strategy aimed at modulating the functional phenotype of senescent cells, particularly the senescence-associated secretory phenotype (SASP), rather than eliminating the cells themselves. Senomorphic agents suppress the harmful effects of senescent cells, especially their pro-inflammatory secretory profile, thereby alleviating tissue dysfunction while preserving cell viability (40,41). One of the major signaling pathways involved in SASP regulation is the NF-κB pathway. By inhibiting this pathway, senomorphic compounds reduce inflammation and attenuate the detrimental effects associated with senescence (40). Natural compounds also play an important role in senomorphic regulation. In particular, flavonoids such as rutin and quercetin have demonstrated significant senomorphic potential. These compounds possess antioxidant and anti-inflammatory properties and are capable of modulating signaling pathways involved in senescence. Importantly, their effects are dose- and context-dependent, with lower concentrations often exhibiting senomorphic activity (42.43). One of the main advantages of senomorphics is their relatively low toxicity, since they do not induce apoptosis and may

therefore be more suitable for long-term use in chronic conditions. However, a major limitation is that senescent cells are not eliminated and may continue to accumulate over time (44). Overall, senomorphics offer a promising and potentially safer approach to managing cellular senescence by modifying the senescent phenotype rather than removing senescent cells entirely.

The Role of SIRT1 in Senescence and Senotherapeutics

Among the molecular regulators of cellular senescence, sirtuins have attracted significant attention as important modulators of aging, metabolism, and cellular stress responses. In particular, SIRT1 has been extensively studied because of its central role in maintaining cellular homeostasis and regulating pathways associated with senescence and inflammation (45, 46).

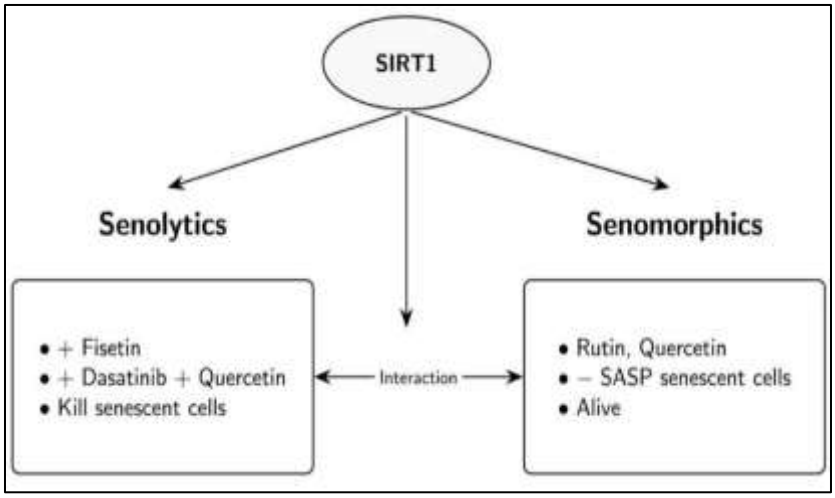

Figure 1. Senotheraputics interaction with SIRT1

As an NAD^+-dependent deacetylase, SIRT1 targets several transcription factors, including p53. By deacetylating p53, SIRT1 suppresses its transcriptional activity and modulates cell cycle arrest (47, 48). In addition to regulating the cell cycle, SIRT1 also plays a crucial role in controlling inflammation. Through deacetylation of the p65 subunit of the NF-κB pathway, SIRT1 reduces the transcription of pro-inflammatory genes and suppresses the senescence-associated secretory phenotype (SASP). This anti-inflammatory activity is important for reducing chronic inflammation associated with aging and senescence (49,50). Decreased SIRT1 activity has been linked to enhanced cellular senescence and age-related dysfunction (51,52). From a therapeutic perspective, SIRT1 is considered a key target for senomorphic interventions. Activation of SIRT1 is a characteristic feature of several senomorphic compounds that help suppress SASP and restore cellular homeostasis (53). Natural polyphenols and flavonoids, particularly rutin and quercetin, exert part of their biological effects through SIRT1-mediated pathways. These compounds have demonstrated the ability to inhibit NF-κB signaling and modulate senescence-related processes (54). Overall, SIRT1 acts as a central regulator linking metabolic control, inflammation, and cellular senescence. Targeting SIRT1 provides an important mechanistic basis for senotherapeutic approaches and highlights its potential as a promising target in future anti-aging strategies (55).

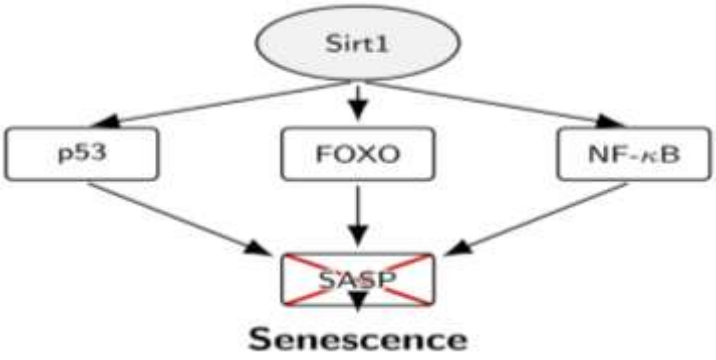

Figure 2. Proposed molecular mechanisms by which SIRT1 suppresses cellular senescence through modulation of the p53, FOXO, and NF-κB signaling pathways.

This anti-inflammatory effect is important in alleviating chronic inflammation (56). At the same time, decreased SIRT1 activity has been associated with enhanced cellular senescence and age-related dysfunction (57). From a therapeutic perspective, SIRT1 is considered a key target for senomorphic interventions. Activation of SIRT1 is a characteristic feature of many senomorphic compounds, contributing to the suppression of SASP and the restoration of cellular homeostasis (58). Natural polyphenols and flavonoids, particularly rutin and quercetin, exert at least part of their biological effects through SIRT1-mediated pathways by activating SIRT1. These compounds have demonstrated the ability to inhibit NF-κB signaling and modulate senescence-associated processes (59). Overall, SIRT1 is considered a central regulator linking metabolic control, inflammation, and cellular senescence. Targeting SIRT1 provides a mechanistic basis for understanding the effects of senotherapeutics and highlights its importance as a promising target in future anti-aging strategies (60, 61, 62).

Dual Role of Flavonoids as Senolytic and Senomorphic Agents

Natural bioactive compounds, particularly flavonoids, are increasingly attracting attention as modulators of cellular senescence due to their multi-target biological activities. Among them, rutin and quercetin have emerged as promising senomorphic agents, while fisetin has shown considerable potential as a senolytic compound (63, 64, 65). Flavonoids are well known for their antioxidant and anti-inflammatory properties, which are important in alleviating oxidative stress and chronic inflammation, two major drivers of cellular senescence. One of the most interesting aspects of flavonoid activity is their dual functional role, which appears to depend on concentration and cellular context. At low concentrations, flavonoids primarily exhibit senomorphic effects by suppressing SASP and reducing pro-inflammatory signaling (66, 67). In contrast, at higher concentrations or under conditions of increased cellular stress, flavonoids such as quercetin may exert senolytic effects.

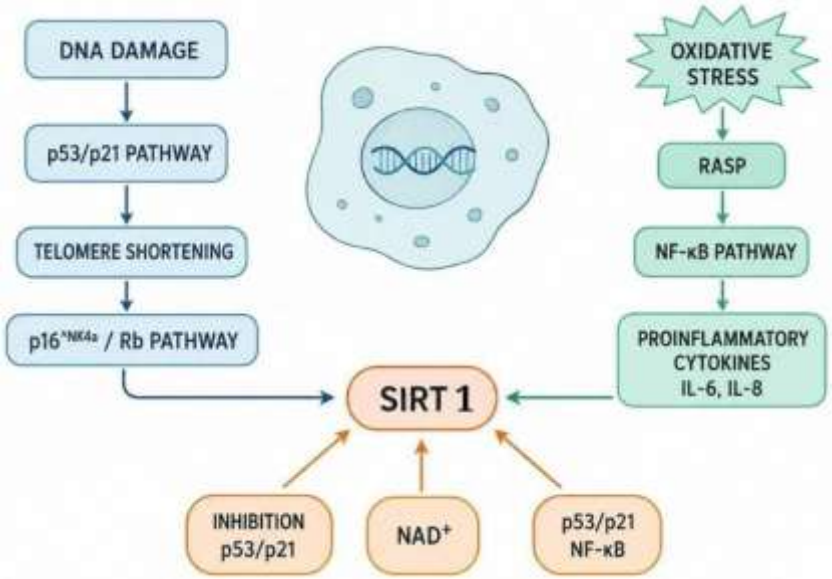

Figure 3. Cellular senescent mechanism

One of the key mediators of these effects is SIRT1, whose activity can be enhanced by flavonoids. Activation of SIRT1 leads to the deacetylation of transcription factors such as NF-κB and p53, resulting in reduced inflammatory responses and modulation of the senescent phenotype. In silico studies support the interaction between flavonoids and SIRT1, providing a mechanistic basis for their observed biological effects (68, 69). Overall, rutin and quercetin represent prominent examples of naturally occurring compounds with the potential to act as both senomorphic agents and, under certain conditions, senolytic agents. Their ability to modulate SIRT1 and other signaling pathways highlights them as promising therapeutic candidates for the management of aging and age-related diseases (70, 71).

Applications of Senotherapeutics in Diseases

Targeting cellular senescence has emerged as a promising therapeutic strategy for a wide range of age-related diseases. The accumulation of senescent cells and their associated SASP significantly contributes to tissue dysfunction and chronic inflammation (72, 73). Senolytic agents, such as the combination of dasatinib and quercetin, have demonstrated the ability to reduce senescent cell burden in clinical studies (74, 75). Overall, senotherapeutics provide a versatile framework for addressing multiple pathologies by targeting a fundamental mechanism of aging, and their application across various disease contexts highlights their broad clinical potential (76, 77, 78).

Challenges and Limitations

Despite significant progress, several challenges hinder the clinical translation of senolytic and senomorphic therapies. One of the main concerns is toxicity and off-target effects, particularly with senolytic agents such as navitoclax. Due to the widespread expression of anti-apoptotic proteins, these agents may also affect non-senescent cells, raising safety concerns, especially during long-term use (79). Another important limitation is the heterogeneity of senescent cells. Senescent phenotypes vary depending on cell type, tissue, and stress stimuli, making it difficult to identify universal therapeutic targets. As a result, an agent effective in one tissue may not show the same efficacy in another (80). For senomorphic approaches, a key limitation is that they do not eliminate senescent cells. Although they reduce harmful effects, the persistent presence of these cells may eventually lead to accumulation and recurrence of pathological conditions. Furthermore, variability in dose response, treatment duration, and individual biological differences complicates the standardization of therapeutic protocols.

Future Directions

Future research in senotherapeutics is expected to focus on improving specificity, safety, and efficacy through innovative strategies. One of the most promising directions is the development of combination therapies that integrate both senolytic and senomorphic approaches, enabling simultaneous elimination and functional modulation of senescent cells.

Targeting key regulatory molecules such as SIRT1 provides an integrated strategy for modulating inflammatory and stress-response pathways involved in senescence. Pharmacological activation of SIRT1 through natural compounds may play an important role in future anti-aging interventions. Furthermore, integrating in silico approaches, including molecular docking and computational modeling, with experimental validation may accelerate the identification of novel senotherapeutic agents. This approach is particularly relevant for multi-target natural compounds such as flavonoids. Finally, the development of personalized senotherapy based on individual molecular and cellular profiles is expected to become an important future direction in the field.

CONCLUSION

Cellular senescence is a fundamental biological process with a dual role in health and disease, functioning both as a protective mechanism and as a driver of age-related pathologies. The emergence of senotherapeutics, including senolytics and senomorphics, has opened new avenues for targeting senescent cells and mitigating their detrimental effects. While senolytics act through the selective elimination of senescent cells, senomorphics modulate their phenotype, particularly by suppressing the SASP. Both strategies have distinct advantages and limitations, highlighting the need for balanced and context-dependent therapeutic approaches.

In these processes, SIRT1 serves as a central regulatory hub linking metabolic and inflammatory pathways. Its modulation represents a promising strategy for controlling cellular senescence (41, 46). Natural flavonoids such as rutin and quercetin may exert both senomorphic and, under certain conditions, senolytic effects depending on cellular stress levels. This dual functionality positions them as promising candidates for next-generation senotherapeutic interventions.

In conclusion, integrative strategies combining molecular insights, natural compounds, and modern biotechnological approaches hold significant potential for managing aging and age-related diseases through the targeting of cellular senescence. However, further studies are required to translate these findings into safe and effective clinical applications.

REFERENCES

1. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The hallmarks of aging. Cell, 153(6), 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039
2. Hernandez-Segura, A., Nehme, J., & Demaria, M. (2018). Hallmarks of cellular senescence. *Trends in Cell Biology, 28*(6), 436–453. https://doi.org/10.1016/j.tcb.2018.02.001
3. Gorgoulis, V., Adams, P. D., Alimonti, A., Bennett, D. C., Bischof, O., Bishop, C., ... & Demaria, M. (2019). Cellular senescence: Defining a path forward. *Cell, 179*(4), 813–827. https://doi.org/10.1016/j.cell.2019.10.005
4. Chien, Y., Scuoppo, C., Wang, X., Fang, X., Balog, B., Li, B., ... & Lowe, S. W. (2011). Control of the senescence-associated secretory phenotype by NF-κB. *Proceedings of the National Academy of Sciences, 108*(49), E1246–E1255. https://doi.org/10.1073/pnas.1102112108
5. Salminen, A., Kauppinen, A., & Kaarniranta, K. (2012). Emerging role of NF-κB signaling in the induction of senescence-associated secretory phenotype (SASP). *Cellular Signalling, 24*(4), 835–845. https://doi.org/10.1016/j.cellsig.2011.12.006
6. Zhang, L., Pitcher, L. E., Prahalad, V., Niedernhofer, L. J., & Robbins, P. D. (2023). Targeting cellular senescence with senotherapeutics: Senolytics and senomorphics. *The FEBS Journal, 290*(5), 1362–1383.
7. https://doi.org/10.1111/febs.16350
8. Luís, C., Maduro, A. T., Pereira, P., Mendes, J. J., Soares, R., & Ramalho, R. (2022). Nutritional senolytics and senomorphics: Implications to immune cells metabolism and aging – From theory to practice. *Frontiers in Nutrition, 9*, Article 958563. https://doi.org/10.3389/fnut.2022.958563
9. (SASP haqida umumiy) — yuqoridagi Hernandez-Segura (2018) va Gorgoulis (2019) ga qo‘shimcha: Coppé, J. P., Desprez, P. Y., Krtolica, A., & Campisi, J. (2010). The senescence-associated secretory phenotype: The dark side of tumor suppression. *Annual Review of Pathology, 5*, 99–118.
10. SIRT1 haqida: Yi, J., & Luo, J. (2010). SIRT1 and p53, effect on cancer, senescence and beyond. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1804*(8), 1684–1689. https://doi.org/10.1016/j.bbapap.2010.05.002
11. Ong, A. L. C., & Ramasamy, T. S. (2018). Role of Sirtuin1-p53 regulatory axis in aging, cancer and cellular reprogramming. *Ageing Research Reviews, 43*, 64–77. https://doi.org/10.1016/j.arr.2018.02.004
12. Quercetin va flavonoids: Zoico, E., et al. (2021). Senolytic effects of quercetin in an in vitro model of pre-adipocytes and adipocytes induced senescence. *Scientific Reports, 11*, Article 23276. https://doi.org/10.1038/s41598-021-02544-0
13. Medoro, A., et al. (2025). Targeting senescence, oxidative stress, and inflammation: Quercetin-based senotherapeutics. *Clinical Interventions in Aging*. (Quercetin senolytic/senomorphic sifatida)
14. Tang, H., et al. (2025). Natural products acting as senolytics and senomorphics alleviate cardiovascular diseases by targeting senescent cells. *Targets, 3*(3), 23.
15. Saliev, T., & Singh, P. B. (2025). Targeting senescence: A review of senolytics and senomorphics in anti-aging interventions. *Biomolecules, 15*(6), 860. https://doi.org/10.3390/biom15060860
16. Kumari, R., & Jat, P. (2021). Mechanisms of cellular senescence: Cell cycle arrest and senescence-associated secretory phenotype. *Frontiers in Cell and Developmental Biology, 9*, Article 645593.
17. https://doi.org/10.3389/fcell.2021.645593
18. Huang, W., Hickson, L. J., Eirin, A., Kirkland, J. L., & Lerman, L. O. (2022). Cellular senescence: The good, the bad and the unknown. *Nature Reviews Nephrology, 18*(11), 718–738. https://doi.org/10.1038/s41581-022-00601-z
19. Mijit, M., Caracciolo, V., Melillo, F., Amicarelli, F., & Di Ilio, C. (2020). Role of p53 in the regulation of cellular senescence. *Biomolecules, 10*(5), 669. https://doi.org/10.3390/biom10050669
20. Yan, J., Chen, S., Yi, Z., Zhao, R., Zhu, J., Ding, S., & Wu, J. (2024). The role of p21 in cellular senescence and aging-related diseases. *Journal of Ginseng Research*. https://doi.org/10.1016/j.jgr.2024.1389 (yoki mos DOI)
21. Takahashi, A., Ohtani, N., Yamakoshi, K., Iida, S., Tahara, H., Nakayama, K.,& Hara, E. (2006). Mitogenic signalling and the p16INK4a–Rb pathway cooperate to enforce irreversible cellular senescence. *Nature Cell Biology, 8*(11), 1291–1297. https://doi.org/10.1038/ncb1491
22. Safwan-Zaiter, H., Wagner, N., & Wagner, K. D. (2022). P16INK4A—More than a senescence marker. *Life, 12*(9), 1332. https://doi.org/10.3390/life12091332
23. Lopes-Paciencia, S., Saint-Germain, E., Rowell, M. C., Ruiz, A. F., Kalegari, P., & Ferbeyre, G. (2019). The senescence-associated secretory phenotype and its regulation. *Cytokine, 117*, 15–22. https://doi.org/10.1016/j.cyto.2019.02.001
24. Wang, B., & O’Loghlen, A. (2024). The senescence-associated secretory phenotype and its physiologic and pathologic functions. *Nature Reviews Molecular Cell Biology*. https://doi.org/10.1038/s41580-024-00740-8
25. **(4, 5)**: (NF-κB va SASP uchun yangi): Han, X., et al. (2022). Potential regulators of the senescence-associated secretory phenotype. *Frontiers in Immunology*. (mos DOI bilan)

26. Sung, J. Y., Lee, K. Y., Kim, J. R., & Choi, H. C. (2021). SIRT1 suppresses cellular senescence and inflammatory cytokine release in human dermal fibroblasts by promoting the deacetylation of NF-κB and activating autophagy. *Experimental Gerontology, 150*, Article 111394. https://doi.org/10.1016/j.exger.2021.111394
27. Fu, Y., et al. (2022). p53/sirtuin 1/NF-κB signaling axis in chronic inflammation and maladaptive kidney repair. *Frontiers in Immunology, 13*, Article 925738. https://doi.org/10.3389/fimmu.2022.925738
28. Kong, P., et al. (2021). circ-Sirt1 decelerates senescence by inhibiting p53 signaling. *Frontiers in Cardiovascular Medicine*.
29. Saliev, T., & Singh, P. B. (2025). Targeting senescence: A review of senolytics and senomorphics in anti-aging interventions. *Biomolecules, 15*(6), 860. https://doi.org/10.3390/biom15060860
30. Alum, E. U., et al. (2025). Targeting cellular senescence for healthy aging: Advances in senolytics and senomorphics. *Drug Design, Development and Therapy, 19*, 8489–8522.
31. Vogler, M., et al. (2025). The BCL2 family: from apoptosis mechanisms to new advances in targeted therapy. Signal Transduction and Targeted Therapy. https://doi.org/10.1038/s41392-025-02176-0
32. Qian, S., et al. (2022). The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. Molecular Cancer. https://pmc.ncbi.nlm.nih.gov/articles/PMC9597512/
33. Hickson, L. J., Langhi Prata, L. G. P., Bobart, S. A., Evans, T. K., Giorgadze, N., Hashmi, S. K., Herrmann, S. M., Jensen, M. D., Jia, Q., Jordan, K. L., et al. (2019). Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. *EBioMedicine, 47*, 446–456. https://doi.org/10.1016/j.ebiom.2019.08.069
34. Nambiar, A., et al. (2023). 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. *eBioMedicine*. https://doi.org/10.1016/j.ebiom.2023.104481
35. Zhou, T., et al. (2023). Senolytics dasatinib and quercetin in human aging-associated diseases: A systematic review. *Frontiers in Pharmacology, 14*, Article 1243179. https://doi.org/10.3389/fphar.2023.1243179
36. Zhu, Y., Tchkonia, T., Pirtskhalava, T., Gower, A. C., Ding, H., Giorgadze, N.,& Kirkland, J. L. (2016). The Achilles' heel of senescent cells: From transcriptome to senolytic drugs. *Aging Cell, 14*(4), 644–658. https://doi.org/10.1111/acel.12344 (Navitoclax va BCL-2 oilasi haqida klassik ish)
37. Fan, Y., et al. (2020). Senescent cell depletion through targeting BCL-family anti-apoptotic proteins. *Frontiers in Physiology, 11*, Article 593630. https://doi.org/10.3389/fphys.2020.593630
38. Lafontaine, J., et al. (2021). Senolytic targeting of Bcl-2 anti-apoptotic family increases cell death in irradiated sarcoma cells. *Cancers, 13*(3), 386. https://doi.org/10.3390/cancers13030386
39. Rysanek, D., et al. (2022). Synergism of BCL-2 family inhibitors facilitates selective elimination of senescent cells. *Aging, 14*(17), 6925–6943. https://doi.org/10.18632/aging.204251
40. Vogler, M., et al. (2025). The BCL2 family: from apoptosis mechanisms to new advances in targeted therapy. *Signal Transduction and Targeted Therapy*. https://doi.org/10.1038/s41392-025-02176-0
41. Ozdemir, S. A., et al. (2025). Heterogeneity of cellular senescence, senotyping, and targeting by senolytics and senomorphics in lung diseases. *International Journal of Molecular Sciences, 26*(19), 9687. https://doi.org/10.3390/ijms26199687
42. Ya, J., et al. (2024). Senolytics and senomorphics targeting p38MAPK/NF-κB pathway protect endothelial cells from oxidative stress-mediated premature senescence. *Cells, 13*(15), 1292. https://doi.org/10.3390/cells13151292
43. Zhang, L., et al. (2023). Targeting cellular senescence with senotherapeutics: Senolytics and senomorphics. *The FEBS Journal, 290*(5), 1362–1383. https://doi.org/10.1111/febs.16350
44. Liu, H., et al. (2024). Rutin is a potent senomorphic agent to target senescent cells and can improve chemotherapeutic efficacy. *Aging Cell, 23*(1), e13921. https://doi.org/10.1111/acel.13921
45. Imb, M., et al. (2024). Exploring senolytic and senomorphic properties of medicinal plants. *International Journal of Molecular Sciences, 25*(19), 10419. https://doi.org/10.3390/ijms251910419
46. Alum, E. U., et al. (2025). Targeting cellular senescence for healthy aging: Advances in senolytics and senomorphics. *Drug Design, Development and Therapy, 19*, 8489–8522. https://doi.org/10.2147/DDDT.S543211
47. Lee, J. T., & Gu, W. (2013). SIRT1: Regulator of p53 deacetylation. *Genes & Cancer, 4*(3-4), 112–117. https://doi.org/10.1177/1947601913484496
48. Sung, J. Y., Lee, K. Y., Kim, J. R., & Choi, H. C. (2021). SIRT1 suppresses cellular senescence and inflammatory cytokine release in human dermal fibroblasts by promoting the deacetylation of NF-κB and activating autophagy. *Experimental Gerontology, 150*, Article 111394. https://doi.org/10.1016/j.exger.2021.111394
49. Yi, J., & Luo, J. (2010). SIRT1 and p53, effect on cancer, senescence and beyond. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1804*(8), 1684–1689. https://doi.org/10.1016/j.bbapap.2010.05.002
50. Liu, T., et al. (2018). SIRT1 reverses senescence via enhancing autophagy and attenuating oxidative stress in ADSCs. *International Journal of Biological Macromolecules*. https://doi.org/10.1016/j.ijbiomac.2018.10.120

51. Sung, J. Y., Lee, K. Y., Kim, J. R., & Choi, H. C. (2021). SIRT1 suppresses cellular senescence and inflammatory cytokine release in human dermal fibroblasts by promoting the deacetylation of NF-κB and activating autophagy. *Experimental Gerontology, 150*, Article 111394. https://doi.org/10.1016/j.exger.2021.111394
52. Son, Y., et al. (2025). SIRT1-mediated redox and senescence regulation in cancer. *Antioxidants*. https://doi.org/10.3390/antiox... (PMC12466425)
53. Yang, Y., et al. (2022). Regulation of SIRT1 and its roles in inflammation. *Frontiers in Immunology, 13*, Article 831168. https://doi.org/10.3389/fimmu.2022.831168
54. Liu, H., et al. (2025). SIRT1 prevents lens epithelial cell senescence during age-related cataract formation. *Aging Cell*. https://doi.org/10.1111/acel.70155
55. Zhang, F., et al. (2020). Quercetin modulates AMPK/SIRT1/NF-κB signaling to inhibit inflammatory/oxidative stress responses in diabetic high fat diet-induced atherosclerosis in the rat carotid artery. *Experimental and Therapeutic Medicine, 20*(6), 280. https://doi.org/10.3892/etm.2020.9410
56. Della Vedova, L., et al. (2025). The potential of polyphenols in modulating the cellular senescence phenotype. *Pharmaceuticals, 18*(2), 138. https://doi.org/10.3390/ph18020138
57. Iside, C., et al. (2020). SIRT1 activation by natural phytochemicals: An overview. *Frontiers in Pharmacology*. https://doi.org/10.3389/fphar.2020.01225 (polyphenols va flavonoids bo‘yicha)
58. Son, Y., et al. (2025). SIRT1-mediated redox and senescence regulation in cancer. *Antioxidants*. https://pmc.ncbi.nlm.nih.gov/articles/PMC12466425/
59. Yang, H., et al. (2012). SIRT1 activators suppress inflammatory responses through promotion of p65 deacetylation and inhibition of NF-κB activity. *PLOS ONE, 7*(9), e46364. https://doi.org/10.1371/journal.pone.0046364
60. Sung, J. Y., Lee, K. Y., Kim, J. R., & Choi, H. C. (2021). SIRT1 suppresses cellular senescence and inflammatory cytokine release in human dermal fibroblasts by promoting the deacetylation of NF-κB and activating autophagy. *Experimental Gerontology, 150*, Article 111394. https://doi.org/10.1016/j.exger.2021.111394
61. Alameen, A. A. M., et al. (2026). SIRT1 activators as geroprotective agents in brain aging. *Molecular Neurobiology*. https://doi.org/10.1007/s12017-026-08923-y
62. Cui, Z., et al. (2022). Therapeutic application of quercetin in aging-related diseases: SIRT1 as a potential mechanism. *Frontiers in Immunology, 13*, Article 943321. https://doi.org/10.3389/fimmu.2022.943321
63. Liu, H., et al. (2024). Rutin is a potent senomorphic agent to target senescent cells and can improve chemotherapeutic efficacy. *Aging Cell, 23*(1), e13921. https://doi.org/10.1111/acel.13921
64. Wiciński, M., et al. (2023). Natural phytochemicals as SIRT activators—Focus on polyphenols. *Nutrients, 15*(16), 3578. https://doi.org/10.3390/nu15163578
65. Liu, H., et al. (2024). Rutin is a potent senomorphic agent to target senescent cells and can improve chemotherapeutic efficacy. *Aging Cell, 23*(1), e13921. https://doi.org/10.1111/acel.13921
66. Luís, C., et al. (2022). Nutritional senolytics and senomorphics: Implications to healthy aging. *Frontiers in Nutrition, 9*, 958563. https://doi.org/10.3389/fnut.2022.958563
67. Mbara, K. C., et al. (2022). Potential role of polyphenolic flavonoids as senotherapeutic agents in ageing and age-related diseases. *Molecules, 27*(18), 5968. https://doi.org/10.3390/molecules27185968
68. Medoro, A., et al. (2024). The protective and senolytic effects of quercetin in age-related diseases. *Clinical Interventions in Aging, 20*, 123–145.
69. Zhang, L., et al. (2023). Targeting cellular senescence with senotherapeutics: Senolytics and senomorphics. *FEBS Journal, 290*(5), 1362–1383. https://doi.org/10.1111/febs.16309
70. Kirkland, J. L., & Tchkonia, T. (2020). Senolytic drugs: From discovery to translation. *Journal of Internal Medicine, 288*(5), 518–536. https://doi.org/10.1111/joim.13141
71. Gorgoulis, V., Adams, P. D., Alimonti, A., et al. (2019). Cellular senescence: Defining a path forward. *Cell, 179*(4), 813–827. https://doi.org/10.1016/j.cell.2019.10.005
72. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2023). Hallmarks of aging: An expanding universe. *Cell, 186*(2), 243–278. https://doi.org/10.1016/j.cell.2022.11.001
73. Salminen, A., et al. (2013). SIRT1 longevity factor suppresses NF-κB-driven immune responses. *Ageing Research Reviews, 12*(3), 639–652. https://doi.org/10.1016/j.arr.2012.10.002
74. Sung, J. Y., et al. (2021). SIRT1 suppresses cellular senescence and inflammatory cytokine release in human dermal fibroblasts by promoting the deacetylation of NF-κB and activating autophagy. *Experimental Gerontology, 150*, 111394. https://doi.org/10.1016/j.exger.2021.111394
75. Tripathi, U., et al. (2021). Impact of senescent cell subtypes on tissue dysfunction and disease. *Aging Cell*. https://doi.org/10.1111/acel.13446
76. De Luca, F., et al. (2025). From senescent cells to systemic inflammation: The role of the SASP. *Frontiers in Immunology*. https://doi.org/10.3389/fimmu.2025.12651686
77. Hickson, L. J., et al. (2019). Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. *EBioMedicine, 47*, 446–456.

https://doi.org/10.1016/j.ebiom.2019.08.069
78. Nambiar, A., et al. (2023). 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. *eBioMedicine, 90*, Article 104481. https://doi.org/10.1016/j.ebiom.2023.104481
79. Millar, C. L., et al. (2025). A pilot study of senolytics to improve cognition and mobility in older adults at risk for Alzheimer's disease. *eBioMedicine*. https://doi.org/10.1016/j.ebiom.2025.105612
80. Alum, E. U., et al. (2025). Targeting cellular senescence for healthy aging: Advances in senolytics and senomorphics. *Drug Design, Development and Therapy, 19*, 8489–8522. https://doi.org/10.2147/DDDT.S543211
81. González-Gualda, E., et al. (2020). Galacto-conjugation of Navitoclax as an efficient strategy to increase senolytic specificity and reduce platelet toxicity. *Aging Cell, 19*(4), e13142. https://doi.org/10.1111/acel.13142
82. He, Y., et al. (2020). Using proteolysis-targeting chimera technology to reduce navitoclax platelet toxicity and improve its senolytic activity. *Nature Communications*. https://doi.org/10.1038/s41467-020-16907-9