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NANOSYSTEMS AS VESICLES FOR DELIVERY OF SENOTHERAPEUTICS FROM NATURAL SOURCES - ADVANTAGES, LIMITATIONS, SCALABILITY, AND ECONOMIC ASPECTS

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Abstract

Leveraging senotherapeutics derived from natural sources is pivotal in advancing senotherapy, offering biocompatible and sustainable solutions to target cellular senescence and mitigate age-related diseases. Nanosystems have emerged as versatile vesicles capable of encapsulating and delivering bioactive agents to senescent cells with high specificity and minimal off-target effects. These nanosystems leverage unique physicochemical properties, such as size, surface charge, and functionalization with targeting ligands, to optimize cellular uptake and therapeutic efficacy. Recent advancements in nanotechnology have facilitated the integration of molecular tools such as senolytics and senomorphics within these carriers, enhancing their ability to selectively clear senescent cells or modulate their secretory phenotype. This review highlights the state-of-the-art in nanosystem development for senotherapeutic applications, addressing their advantages, limitations, scalability, economic aspects, regulatory approval, and long-term effects. This work underscores the transformative potential of nanosystems in senotherapeutic delivery and advocates for continued interdisciplinary collaboration to overcome existing barriers and realize their full therapeutic potential.

Key words*: senotherapeutics, nanosystems, delivery.*

INTRODUCTION

Cellular senescence, characterized by irreversible cell cycle arrest, contributes to aging and various age-related pathologies, including Alzheimer`s disease, atherosclerosis, and type 2 diabetes, etc. (Boccardi and Mecocci, 2021). Senotherapy, the administration of senotherapeutic substances - senolytics and senomorphics, is an emerging field of research for the development of potential treatments and strategies that specifically target cellular senescence. While senolytics function by selectively eliminating senescent cells, senomorphics focus on modulating the senescence-associated secretory phenotype (SASP) to preserve cellular homeostasis. Senolytics act by disrupting the molecular pathways that allow senescent cells to evade apoptosis. These pathways commonly involve key regulatory proteins, including p53, p21, FOXO4, PI3K, Bcl-2 family proteins, etc. By inhibiting pro-survival mechanisms, senolytic compounds facilitate the clearance of dysfunctional senescent cells, thereby mitigating their deleterious effects on aging tissues (Zhu et al., 2015). Senomorphic agents suppress key signaling pathways that regulate senescence, such as NF-κB, mTOR, IL-1α, and p38 MAPK, which play central roles in SASP regulation. Specifically, NF-κB and IL-1α are key regulators of the SASP, promoting the expression of pro-inflammatory cytokines. chemokines, and proteases (Liang et al., 2021; Salminen et al., 2012; Chien et al., 2011; Fruend et al., 2010), mTOR signaling increase SASP production and reinforces the senescent phenotype (Laberge et al., 2015), while p38 MAPK is activated in response to stress and contributes to both cell cycle arrest and SASP induction (Freund et al., 2011). Together, these pathways are crucial in maintaining the senescent state. In addition to SASP inhibition, certain senomorphics may also modulate other markers of senescence, preserving cellular function and delaying the onset of age-related

deterioration (Kritsilis et al., 2018; Evangelou et al., 2017; Van Deursen, 2014).

Natural products, abundant in bioactive compounds, present a valuable reservoir for potential senotherapeutic agents, having mainly senomorphic properties, and a few display senolytic effects. Senolytic substances from natural sources are: quercetin (Zhu et al., 2015), dasatinib (Zhu et al., 2015), piperlongumin (Wang, 2016; Bogan and Brenner, 2008), fisetin (Lagoumtzi & Chondrogianni, 2021; Yousefzadeh et al., 2018; Zhu et al., 2017), curcumin (Bielak-Zmijewska et al., 2019; Li et al., 2019). Examples of senomorphic substances from natural sources include: epigallocatechin gallate (Zhu et al., 2015), resveratrol (Kulkarni and Cantó, 2015), apigenin (Lim et al., 2015), kaempferol (Lim et al., 2015), genistein, berberine (Zhang et al. 2022), ouabain, digoxin, 4,4′-dimethoxychalcone (Zhang et al. 2021). However, their therapeutic efficacy is often hindered due to bioavailability. Leveraging senotherapeutics derived from natural sources is pivotal in advancing senotherapy, offering biocompatible and sustainable solutions to target cellular senescence and combat age-related diseases (Kirkland & Tchkonia, 2020).

Nanosystems have emerged as versatile carriers, capable of efficiently encapsulating and delivering bioactive compounds to senescent cells with high precision and minimal unintended effects. These systems exploit key physicochemical properties, such as size, surface charge, and functionalization with targeting ligands, to enhance cellular uptake and therapeutic impact. Recent progress in nanotechnology has enabled the incorporation of senotherapeutics into these carriers, improving their capacity to selectively eliminate senescent cells or regulate their secretory activity (Squillaro et al., 2018). To date, only a limited number of nanosystems designed for delivering active substances to senescent cells have been reported in the literature. Examples include mesoporous silica nanoparticles coated with galactooligosaccharides (GosNPs) of varying lengths, GalNPs, calcium carbonate nanoparticles conjugated with monoclonal antibody CD9 and coated with lactose-polyethylene glycol (CD9-Lac/CaCO3 NPs), and molybdenum disulfide nanoparticles (MoS2) (Adamczyk-Grochala and Lewinska, 2020). Current research indicates that the development of nanosystems targeting senescent cells is still in its early stages, making all advancements in this field highly impactful for both the scientific and medical communities.

This review highlights the state-of-the-art in nanosystem development for senotherapeutic applications, addressing their advantages, limitations, scalability, economic aspects, regulatory approval, and long-term effects.

MATERIALS AND METHODS

This paper is based on secondary research through a literature search and analysis of papers related to nanotechnology-based delivery systems for senotherapeutics conducted in March 2025. The search was performed using the bibliometric database Scopus and keywords used included: "senescence", "senescent cells", "senotherapy", "senotherapeutic", "senolytics", "senomorphic", "nanovehicles", "nanosystems" and "senotherapeutic delivery". Inclusion criteria included just research articles and reviews published from 2005 to 2025. Other types like books, book chapters, conference papers, online articles ahead of print, and retracted papers were excluded. Only papers published in English were included in the search. After the inclusion and exclusion steps, 316 articles were selected from Scopus. From these 55 articles were most selected relevant for this review taking into consideration studies published in high-impact journals and to those offering experimental validation of concepts related to senolytic or senomorphic agents from natural sources and nanotechnology-based delivery methods. The full-text articles were consulted from ScienceDirect and PubMed databases

RESULTS AND DISCUSSIONS

Nanosystems in the Delivery of Senotherapeutics from Natural sources: Potential and Advances

Given the current scientific landscape, there is a growing need to explore innovative methods for addressing cellular senescence through

more efficient senotherapeutic delivery. Consequently, the development of nanosystems capable of controlled release and targeted administration of senolytic and senomorphic agents represents both a critical opportunity and an urgent necessity. Nanosystems provide precise targeting, controlled release, and improved cellular uptake. By tailoring nanosystems based on specific attributes - such as size, shape, and surface charge - senolytic or senomorphic compounds can be directed toward senescent cells while reducing collateral damage to healthy tissues. Furthermore, encapsulating senotherapeutic agents within nanocarriers shields them from premature degradation, thereby increasing their stability and bioavailability (Obeid et al., 2017; Squillaro et al., 2018).

An innovative approach involves smart nanocarriers engineered to release senolytic agents in response to senescence-associated biomarkers, such as senescence-associated beta-galactosidase (SA-β-gal), which is highly expressed in senescent cells (Adamczyk-Grochala & Lewinska, 2020; Lee et al., 2006). One of the nanosystems developed for targeted senolytic delivery consists of mesoporous silica nanoparticles functionalized with galacto-oligosaccharides and loaded with rhodamine B, where uptake by human senescent cells activates the release mechanism in response to SA-β-gal (Agostini et al., 2012). Further research has demonstrated the efficacy of β (1,4)-galacto-oligosaccharide-coated nanoparticles loaded with navitoclax, a well-known senolytic agent, in selectively eliminating senescent cells induced by DNA damage or chemotherapy (Muñoz-Espín et al., 2018). Additionally, the conjugation of therapeutic molecules with nanostructures has shown potential senomorphic effects, particularly by modulating and suppressing the SASP (Thapa et al., 2017; Lewinska et al., 2020).

Recent studies have explored nanocarrier-based approaches targeting the CD9 receptor, which is overexpressed in aging cells. One *in vitro* study demonstrated that nanoparticles functionalized with an anti-CD9 monoclonal antibody and loaded with rapamycin, a well-established mTOR inhibitor with anti-aging effects, effectively counteracted cellular senescence (Thapa et al., 2017). In a related approach, PEGylated liposomes targeting CD9 exhibited preferential uptake in prematurely senescent human dermal fibroblasts compared to younger fibroblasts, underscoring their potential as a senotherapeutic delivery system (Nguyen et al., 2017). Further investigations into rapamycin-loaded nanoparticles targeting CD9-overexpressing cells revealed that rapamycin not only promoted cellular proliferation but also reduced the proportion of SA-β-gal-positive senescent cells (Nguyen et al., 2017). Additionally, molybdenum disulfide (MoS_2) nanoparticles have been shown to counteract hydrogen-peroxide-induced senescence in endothelial cells (Ke et al., 2018). The successful application of these nanosystems in delivering synthetic senolytics suggests that similar strategies could be extended to senotherapeutic agents derived from natural sources. Several nanotechnology-based strategies have been explored for the targeted delivery of compounds such as fisetin, quercetin, resveratrol, curcumin, and dasatinib, offering promising avenues for targeting senescence or treating senescence-related diseases. For instance, magnetite nanoparticles conjugated with quercetin (MNPQ) have demonstrated both senolytic and senostatic activity in human fibroblasts subjected to premature senescence via hydrogen peroxide exposure. *In vitro* experiments confirmed that MNPQ nanoparticles effectively cleared senescent fibroblasts, while also reducing the pro-inflammatory response associated with senescence, as evidenced by decreased secretion of IL-8 and IFN-β, alongside AMP-activated protein kinase activation (Lewinska et al., 2020).

Nano-molecularly imprinted nanoparticles (70–200 nm) loaded with dasatinib successfully reduced the number of senescent bladder cancer cells (Ekpenyong-Akiba et al., 2019). Additionally, dasatinib combined with quercetin in WAT-targeted liposomes (145 nm) demonstrated potent senolytic activity, eliminating senescent cells and reducing lipolysis. This formulation exhibited a controlled release, with over 80% of dasatinib and nearly all quercetin steadily released over 50 hours without burst effects (Tang et al., 2024). Also, fusogenic liposomes demonstrated efficient resveratrol delivery into cerebromicro-

vascular endothelial cells isolated from aged rats, triggering rapid activation of Nrf2-driven antioxidant defenses (Csiszár et al., 2015). Notably, dendritic polymer nanoparticles (<200 nm) co-loaded with curcumin and resveratrol exhibited a synergistic effect in neuroblastoma, inducing mitochondrial disruption, affecting intracellular calcium release, and promoting cancer cell death through slow-release kinetics (Ben-Zichri et al., 2022).

Beyond these advances, various nanocarrier systems, including nanosuspensions, carbon nanotubes, polymeric micelles, and lipid-based nanoparticles such as liposomes, solid lipid nanoparticles, nanoemulsions, and nanostructured lipid carriers - have been extensively investigated to enhance the solubility and bioavailability of natural compounds like resveratrol, curcumin, quercetin, epigallocatechin gallate (EGCG), and fisetin. However, their potential for senotherapeutic applications remains largely unexplored (Nagesh et al., 2019; Obeid et al., 2017; Squillaro et al., 2018).

Advantages and Limitations of Nanosystems in the Delivery of Senotherapeutics from Natural sources

One of the key benefits of nanosystems in the delivery of senotherapeutics derived from natural sources is enhanced bioavailability, as nanovesicles improve the solubility and stability of hydrophobic compounds, ensuring their efficient absorption and prolonged circulation in the body. This is particularly important for natural compounds, many of which have poor water solubility and limited bioavailability in their free form. Additionally, targeted delivery is a crucial advantage of nanosystems, as surface modifications allow for receptor-mediated targeting, ensuring that the therapeutic payload reaches specific cells or tissues. This targeted approach minimizes damage to healthy cells and maximizes the efficacy of senotherapeutics (Obeid et al., 2017; Adamczyk-Grochala & Lewinska, 2020).

Another major benefit of nanosystems is their ability to provide controlled and sustained drug release. By engineering nanovesicles to respond to physiological stimuli such as pH, temperature, or enzymatic activity, the release of therapeutic agents can be precisely regulated, reducing the frequency of administration and improving patient compliance. Furthermore, reduced toxicity is a significant advantage, as encapsulation of the active ingredient within nanocarriers prevents premature degradation and minimizes off-target effects, thereby reducing systemic toxicity and unwanted side effects (Squillaro et al., 2018; Lee et al., 2006).

Despite these advantages, nanosystems also face several limitations that hinder their widespread application. One major challenge is physical instability, as nanovesicles are prone to aggregation, fusion, or leakage of the encapsulated drugs, which can compromise their efficacy and shelf life. This instability can result in unpredictable drug release profiles and reduced therapeutic effects. Moreover, the complex manufacturing process of nanovesicles adds to the difficulty of their large-scale production. The preparation of these nanosystems often requires specialized equipment, precise formulation techniques, and strict quality control measures, making production costly and time-consuming (Adamczyk-Grochala & Lewinska, 2020; Herdiana et al. 2022).

In addition, regulatory challenges present a significant barrier to the clinical translation of nanotechnology-based therapeutics. The approval process for these advanced delivery systems involves rigorous safety and efficacy evaluations, requiring extensive preclinical and clinical testing. This regulatory scrutiny can lead to long development timelines and high costs, slowing down the commercialization of nanosystem-based senotherapeutics (Baig et al., 2021).

Scalability, economic viability of nanosystems as vesicles for delivering senotherapeutics from natural sources

The large-scale production and commercialization of nanosystems as vesicles for delivering senotherapeutics from natural sources present significant challenges in terms of scalability and economic viability. While nanotechnology-based drug delivery systems have demonstrated remarkable potential in preclinical studies, their transition from laboratory research to industrial-scale production requires overcoming several technological and economic barriers (Herdiana et al. 2022).

Scalability is a crucial factor in the successful implementation of nanosystems for therapeutic applications. The production of nanocarriers, such as liposomes, polymeric nanoparticles, and lipid-based nanovesicles, involves synthesis methods like high-pressure homogenization, solvent evaporation, and microfluidic techniques. Scaling up these processes while maintaining the physicochemical properties, drug loading efficiency, and stability of the nanosystems is a major challenge (Baig et al., 2021). Additionally, batch-to-batch reproducibility and sterility assurance are critical for ensuring consistent therapeutic efficacy and safety. The development of robust, cost-effective, and automated production systems is essential to meet the demand for large-scale manufacturing (Leong et al., 2019).

From an economic perspective, the high cost of raw materials, production technologies, and quality control measures poses a significant challenge. The complexity of nanosystem fabrication often leads to increased manufacturing expenses, limiting their accessibility, particularly for natural compounds with low-cost alternatives. Moreover, the cost-benefit ratio of using nanosystems for delivering senotherapeutics must be carefully assessed, considering factors such as prolonged shelf life, reduced dosage frequency, and improved therapeutic outcomes. Investment in research and development, as well as strategic partnerships between academia, pharmaceutical industries, and biotech firms, can help drive cost-effective innovations in nanosystem production (Ali et al., 2022).

Long-term effects and Regulatory approval concerns

The long-term effects of using nanosystems as vesicles for the delivery of senotherapeutics from natural sources remain a critical area of investigation, particularly regarding their safety, efficacy, and impact on biological systems over extended periods. While nanosystems offer numerous advantages, such as enhanced bioavailability, targeted drug delivery, and controlled release, their prolonged use raises concerns about biocompatibility, toxicity, immune responses, and potential bioaccumulation. One of the most important considerations for the long-term application of nanosystems is their biocompatibility. While many nanocarriers, including lipid-based nanoparticles, polymeric nanoparticles, and mesoporous silica nanoparticles, have demonstrated safety in short-term studies, their prolonged exposure in biological systems could lead to unforeseen toxic effects. The composition of these nanosystems, their degradation products, and their interaction with cellular components may contribute to cytotoxicity, oxidative stress, or inflammation. This raises concerns about bioaccumulation in tissues, particularly in the liver, kidneys, and spleen, which are responsible for nanoparticle clearance. The long-term retention of these materials could interfere with normal organ function and contribute to adverse health outcomes (Choi et al., 2022).

To address these long-term concerns, ongoing research is focused on optimizing nanosystem designs to enhance their biodegradability, minimize toxicity, and improve clearance mechanisms. Advanced *in vitro* and *in vivo* models, as well as long-term clinical studies, are essential to evaluating the sustained effects of these technologies (Adamczyk-Grochala & Lewinska, 2020).

Regulatory approval remains one of the most significant hurdles in bringing nanosystem-based senotherapeutics to the market. Regulatory agencies like European Medicines Agency (EMA) have stringent guidelines for evaluating nanomedicines, requiring extensive preclinical and clinical data on their safety, efficacy, pharmacokinetics, and potential toxicity. Standardized protocols for characterizing nanosystems, assessing their stability, and evaluating their interactions with biological systems are needed to facilitate regulatory approvals (Choi et al., 2022). Within the EU, the EMA has issued reflection papers emphasizing a case-by-case evaluation of nanotechnology-based medicinal products and encouraging early scientific dialogue with developers (EMA, 2025). However, the lack of specific regulatory frameworks tailored to senotherapeutics and the diversity of nanosystems complicate harmonization efforts.

Globally, agencies such as the U.S. Food and Drug Administration (FDA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) also adopt cautious, data-intensive

approaches. The FDA's draft guidance highlights the importance of thorough physicochemical characterization, assessment of biocompatibility, and comparative evaluation with conventional formulations (FDA, 2017). While regulatory convergence is progressing through ICH guidelines such as Q8 to Q10, significant gaps remain, particularly in defining validated biomarkers of cellular senescence and ensuring long-term safety surveillance (ICH, 2009). Therefore, early engagement with regulatory bodies, robust quality-by-design (QbD) strategies, and transparent reporting of nanosystem behavior in complex biological environments are essential to accelerate the clinical translation and market access of nanosystem-based senotherapeutics.

CONCLUSIONS

Nanosystems-based senotherapeutics derived from natural compounds are a promising approach to combat senescence and age-related diseases. While nanosytems have great potential, their long-term safety remains challenging. It is critical to elucidate how these carriers interact with the immune system and how they are metabolized or cleared from the body. Progress in nanotechnology and evolving regulatory frameworks will help to move these systems closer to clinical application. However, translating them into scalable and safe therapies will require close collaboration among researchers, industry representatives, and regulatory agencies.

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REFERENCES

Adamczyk-Grochala, J., & Lewinska, A. (2020). Nano-based theranostic tools for the detection and elimination of senescent cells. *Cells, 9*(12), 2659. https://doi.org/10.3390/cells9122659

Agostini, A., Mondragón, L., Bernardos, A., Martínez-Máñez, R., Marcos, M.D., Sancenón, F., Soto, J., Costero, A., Manguan-García, C., Perona, R., Moreno-Torres, M., Aparicio-Sanchis, R., & Murguía, J.R. (2012). Targeted cargo delivery in senescent cells using capped mesoporous silica nanoparticles. *Angewandte Chemie International Edition, 51*, 10556–10560. https://doi.org/10.1002/anie.201204663

Ali, A. M. M., Jabir, S. M., Kadhim, A. A. & Almagtome, A. (2022). Nanotechnology practices and cost restructure for effective cost management under Industry 4.0-based manufacturing systems. *TEM Journal, 11*(3), 1193-1199. https://doi.org/10.18421/TEM113-26.

Baig, N., Kammakakam, I. & Falath, W. (2021). Nanomaterials: a review of synthesis methods, properties, recent progress, and challenges. *Materials Advances, 2*, 1821-1871. https://doi.org/10.1039/d0ma00807a.

Ben-Zichri, S., Meltzer, M., Lacham-Hartman, S., Kolusheva, S., Hadad, U., Papo, N., & Jelinek, R. (2022). Synergistic activity of anticancer polyphenols embedded in amphiphilic dendrimer nanoparticles. *ACS Applied Polymer Materials, 4*(12), 8913–8925. https://doi.org/10.1021/acsapm.2c01316

Bielak-Zmijewska, A., Grabowska, W., Ciolko, A., Bojko, A., Mosieniak, G., Bijoch, Ł., & Sikora, E. (2019). The role of curcumin in the modulation of ageing. *International Journal of Molecular Sciences, 20*(5), 1239. https://doi.org/10.3390/ijms20051239

Boccardi, V., & Mecocci, P. (2021). Senotherapeutics: Targeting senescent cells for the main age-related diseases. *Mechanisms of Ageing and Development, 197*, 111526. https://doi.org/10.1016/j.mad.2021.111526

Bogan, K.L., & Brenner, C. (2008). Nicotinic acid, nicotinamide, and nicotinamide riboside: A molecular evaluation of NAD+ precursor vitamins in human nutrition. *Annual Review of Nutrition, 28*, 115–130. https://doi.org/10.1146/annurev.nutr.28.061807.155443

Chien, Y., Scuoppo, C., Wang, X., Fang, X., Balgley, B., Bolden, J. E., Premsrirut, P., Luo, W., Chicas, A., Lee, C. S., Kogan, S. C., & Lowe, S. W. (2011). Control of the senescence-associated secretory phenotype by NF-κB promotes senescence and enhances chemosensitivity. *Genes & Development, 25*(20), 2125–2136. https://doi.org/10.1101/gad.17276711

Choi, J. Y., Yee, S. F., Tchangalova, T., Yang, G. & Fisher, J. P. (2022). Recent advances in senotherapeutics delivery. *Tissue Engineering Part B: Reviews, 28*(6), 1223–1234. https://doi.org/10.1089/ten.TEB.2021.0212.

Csiszár, A., Csiszar, A., Pinto, J. T., Gautam, T., Kleusch, C., Hoffmann, B., Tucsek, Z., Toth, P., Sonntag, W. E., & Ungvari, Z. (2015). Resveratrol encapsulated in novel fusogenic liposomes activates Nrf2 and attenuates oxidative stress in cerebromicrovascular endothelial cells from aged rats. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 70*(3), 303–313. https://doi.org/10.1093/gerona/glu029

Ekpenyong-Akiba, A. E., Canfarotta, F., Abd, H. B., Poblocka, M., Casulleras, M., Castilla-Vallmanya, L., Kocsis-Fodor, G., Kelly, M. E., Janus, J., Althubiti, M., Piletska, E., Piletsky, S., & Macip, S. (2019). Detecting and targeting senescent cells using molecularly imprinted nanoparticles. *Nanoscale Horizons, 4*(3), 757–768. https://doi.org/10.1039/C8NH00473K

EMA (2025). Nanotechnology-based medicinal products for human use EU-IN Horizon Scanning Report January 2025, European Medicines Agency/20989/2025. [online] Available at: https://www.ema.europa.eu/en/documents/report/nanotechnology-based-medicinal-products-human-use-eu-horizon-scanning-report_en.pdf [Accessed 23 Mar. 2025]

Evangelou, K., Lougiakis, N., Rizou, S. V., Kotsinas, A., Kletsas, D., Muñoz-Espín, D., Kastrinakis, N. G., Pouli, N., Marakos, P., Townsend, P., Serrano, M., Bartek, J., & Gorgoulis, V. G. (2017). Robust, universal biomarker assay to detect senescent cells in biological specimens. *Aging Cell, 16*, 192–197. https://doi.org/10.1111/acel.12545

FDA (2017). Drug Products, Including Biological Products, that Contain Nanomaterials – Draft Guidance for Industry. U.S. Food and Drug Administration. [online] Available at: https://www.fda.gov/media/109910/download [Accessed 23 Mar. 2025]

Freund, A., Orjalo, A. V., Desprez, P. Y., & Campisi, J. (2010). Inflammatory networks during cellular senescence: causes and consequences. *Trends in Molecular Medicine, 16*(5), 238–246. https://doi.org/10.1016/j.molmed.2010.03.003

Freund, A., Patil, C. K., & Campisi, J. (2011). p38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. *The EMBO Journal, 30*(8), 1536–1548. https://doi.org/10.1038/emboj.2011.69

Herdiana, Y., Wathoni, N., Shamsuddin, S. & Muchtaridi, M. (2022). Scale-up polymeric-based nanoparticles drug delivery systems: Development and challenges. *OpenNano, 7*, 100048. https://doi.org/10.1016/j.onano.2022.100048.

ICH (2009). ICH Harmonised Tripartite Guideline: Pharmaceutical Quality System Q10. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. [online] Available at: https://database.ich.org/sites/default/files/Q10_Guideline.pdf [Accessed 23 Mar. 2025].

Ke, S., Lai, Y., Zhou, T., Li, L., Wang, Y., Ren, L., & Ye, S. (2018). Molybdenum disulfide nanoparticles resist oxidative stress-mediated impairment of autophagic flux and mitigate endothelial cell senescence and angiogenic dysfunctions. *ACS Biomaterials Science & Engineering, 4*, 663–674. https://doi.org/10.1021/acsbiomaterials.7b00714

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

Kritsilis, M., Rizou, S. V., Koutsoudaki, P. N., Evangelou, K., Gorgoulis, V. G., & Papadopoulos, D. (2018). Ageing, cellular senescence and neurodegenerative disease. *International Journal of Molecular Sciences, 19*, E2937. https://doi.org/10.3390/ijms19102937

Kulkarni, S. S., & Cantó, C. (2015). The molecular targets of resveratrol. *Biochimica et Biophysica Acta, 1852*, 1114–1123. https://doi.org/10.1016/j.bbadis.2014.10.005

Laberge, R. M., Sun, Y., Orjalo, A. V., Patil, C. K., Freund, A., Zhou, L., Curran, S. C., Davalos, A. R., Wilson-Edell, K. A., Liu, S., Limbad, C., Demaria, M., Li, P., Hubbard, G. B., Ikeno, Y., Javors, M., Desprez, P. Y., Benz, C. C., Kapahi, P., Nelson, P. S., Campisi, J. (2015). MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. *Nature Cell Biology, 17*(8), 1049–1061. https://doi.org/10.1038/ncb3195

Lagoumtzi, S. M., & Chondrogianni, N. (2021). Senolytics and senomorphics: Natural and synthetic therapeutics in the treatment of aging and chronic diseases. *Free Radical Biology and Medicine, 171*, 169–190. https://doi.org/10.1016/j.freeradbiomed.2021.05.003

Lee, B. Y., Han, J. A., Im, J. S., Morrone, A., Johung, K., Goodwin, E. C., Kleijer, W. J., DiMaio, D., & Hwang, E. S. (2006). Senescence-associated β-galactosidase is lysosomal β-galactosidase. *Aging Cell, 5*, 187–195. https://doi.org/10.1111/j.1474-9726.2006.00199.x

Leong, H.S.; Butler, K.S.; Brinker, C.J.; Azzawi, M.; Conlan, S.; Dufés, C.; Owen, A.; Rannard, S.; Scott, C.; Chen, C.; Dobrovolskaia, M.A.; Kozlov, S.V.; Prina-Mello, A.; Schmid, R.; Wick, P.; Caputo, F.; Boisseau, P.; Crist, R.M.; McNeil, S.E.; Fadeel, B.; Tran, L.; Hansen, S.F.; Hartmann, N.B.; Clausen, L.P.W.; Skjolding, L.M.; Baun, A.; Ågerstrand, M.; Gu, Z.; Lamprou, D.A.; Hoskins, C.; Huang, L.; Song, W.; Cao, H.; Liu, X.; Jandt, K.D.; Jiang, W.; Kim, B.Y.S.; Wheeler, K.E.; Chetwynd, A.J.; Lynch, I.; Moghimi, S.M.; Nel, A.; Xia, T.; Weiss, P.S.; Sarmento, B.; das Neves, J.; Santos, H.A.; Santos, L.; Mitragotri, S.; Little, S.; Peer, D.; Amiji, M.M.; Alonso, M.J.; Petri-Fink, A.; Balog, S.; Lee, A.; Drasler, B.; Rothen-Rutishauser, B.; Wilhelm, S.; Acar, H.; Harrison, R.G.; Mao, C.; Mukherjee, P.; Ramesh, R.; McNally, L.R.; Busatto, S.; Wolfram, J.; Bergese, P.; Ferrari, M.; Fang, R.H.; Zhang, L.; Zheng, J.; Peng, C.; Du, B.; Yu, M.; Charron, D.M.; Zheng, G. & Pastore, C. (2019). On the issue of transparency and reproducibility in nanomedicine. *Nature nanotechnology*, *14*(7), 629–635. https://doi.org/10.1038/s41565-019-0496-9

Lewinska, A., Adamczyk-Grochala, J., Bloniarz, D., Olszowka, J., Kulpa-Greszta, M., Litwinienko, G., Tomaszewska, A., Wnuk, M., & Pazik, R. (2020). AMPK-mediated senolytic and senostatic activity of quercetin surface-functionalized Fe_3O_4 nanoparticles during oxidant-induced senescence in human fibroblasts. *Redox Biology, 28*, 101337. https://doi.org/10.1016/j.redox.2019.101337

Li, W., He, Y., Zhang, R., Zheng, G., & Zhou, D. (2019). The curcumin analog EF24 is a novel senolytic agent. *Aging (Albany NY, 11*, 771–782. https://doi.org/10.18632/aging.101787

Liang, Y., Liang, N., Ma, Y., Tang, S., Ye, S., & Xiao, F. (2021). Role of Clusterin/NF-κB in the secretion of senescence-associated secretory phenotype in Cr(VI)-induced premature senescent L-02 hepatocytes. *Ecotoxicology and Environmental Safety, 219*, 112343. https://doi.org/10.1016/j.ecoenv.2021.112343

Lim, H., Park, H., & Kim, H. P. (2015). Effects of flavonoids on senescence-associated secretory phenotype formation from bleomycin-induced senescence in BJ fibroblasts. *Biochemical Pharmacology, 96*(4), 337–348. https://doi.org/10.1016/j.bcp.2015.06.013

Muñoz-Espín, D., Rovira, M., Galiana, I., Giménez, C., Lozano-Torres, B., Paez-Ribes, M., Llanos, S., Chaib, S., Muñoz-Martín, M., Ucero, A. C., Garaulet, G., Mulero, F., Dann, S., VanArsdale, T., Shields, D., Bernardos, A., Murguía, J. R., Martínez-Máñez, R., & Serrano, M. (2018). A versatile drug delivery system targeting senescent cells. *EMBO Molecular Medicine, 10*, e9355. https://doi.org/10.15252/emmm.201809355

Nagesh, P. K. B., Chowdhury, P., Hatami, E., Kumari, S., Kashyap, V. K., Tripathi, M. K., Wagh, S., Meibohm, B., Chauhan, S. C., Jaggi, M., & Yallapu, M. (2019). Cross-linked polyphenol-based drug nano-self-assemblies engineered to blockade prostate cancer senescence. *ACS Applied Materials & Interfaces, 11*, 38537–38554. https://doi.org/10.1021/acsami.9b14738

Nguyen, H. T., Thapa, R. K., Shin, B. S., Jeong, J.-H., Kim, J.-R., Yong, C. S., & Kim, J. O. (2017). CD9 monoclonal antibody-conjugated PEGylated liposomes for targeted delivery of rapamycin in the treatment of cellular senescence. *Nanotechnology, 28*, 095101. https://doi.org/10.1088/1361-6528/aa57b3

Obeid, M. A., Al Qaraghuli, M. M., Alsaadi, M., Alzahrani, A. R., Niwasabutra, K., & Ferro, V. A. (2017). Delivering natural products and biotherapeutics to improve drug efficacy. *Therapeutic Delivery, 8*, 947–956. https://doi.org/10.4155/tde-2017-0060

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

Squillaro, T., Cimini, A., Peluso, G., Giordano, A., & Melone, M. A. B. (2018). Nano-delivery systems for encapsulation of dietary polyphenols: An experimental approach for neurodegenerative diseases and brain tumors. *Biochemical Pharmacology, 154*, 303–317. https://doi.org/10.1016/j.bcp.2018.05.016

Tang, Q., Xing, X., Huang, H., Yang, J., Li, M., Xu, X., Gao, X., Liang, C., Tian, W., & Liao, L. (2024). Eliminating senescent cells by white adipose tissue–targeted senotherapy alleviates age-related hepatic steatosis through decreasing lipolysis. *GeroScience, 46*, 3149–3167. https://doi.org/10.1007/s11357-024-01068-5

Thapa, R. K., Nguyen, H. T., Jeong, J.-H., Kim, J. R., Choi, H.-G., Yong, C. S., & Kim, J. O. (2017). Progressive slowdown/prevention of cellular senescence by CD9-targeted delivery of rapamycin using lactose-wrapped calcium carbonate nanoparticles. *Scientific Reports, 7*, 43299. https://doi.org/10.1038/srep43299

Van Deursen, J. M. (2014). The role of senescent cells in ageing. *Nature, 509*(7501), 439–446. https://doi.org/10.1038/nature13193

Vázquez, O. S. B., Magos-Guerrero, G. A., Escobar Ramírez, J. L., & Gomez-Verjan, J. C. (2022). Natural products as a major source of candidates for potential senolytic compounds obtained by in silico screening. *Medicinal Chemistry*, 1–16. https://doi.org/10.2174/1573406419666221019153537

Wang, Y., Chang, J., Liu, X., Zhang, X., Zhang, S., Zhang, X., Zhou, D., & Zheng, G. (2016). Discovery of piperlongumine as a potential novel lead for the development of senolytic agents. *Aging (Albany NY)*, *8*, 2915. https://doi.org/10.18632/aging.101100

Yousefzadeh, M. J., Zhu, Y., McGowan, S. J., Angelini, L., Fuhrmann-Stroissnigg, H., Xu, M., Ling, Y. Y., Melos, K. I., Pirtskhalava, T., Inman, C. L., McGuckian, C., Wade, E. A., Kato, J. I., Grassi, D., Wentworth, M., Burd, C. E., Arriaga, E. A., Ladiges, W. L., Tchkonia, T., Kirkland, J. L., Robbins, P. D., & Niedernhofer, L. J. (2018). Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine*, *36*, 18–28. https://doi.org/10.1016/j.ebiom.2018.09.015

Zhang, Q., Li, S., Chen, F., Zeng, R., & Tong, R. (2022). Targeted delivery strategy: A beneficial partner for emerging senotherapy. *Biomedicine & Pharmacotherapy*, *155*, 113737. https://doi.org/10.1016/j.biopha.2022.113737

Zhang, L., Pitcher, L. E., Prahalad, V., Niedernhofer, L. J., & Robbins, P. D. (2021). Recent advances in the discovery of senolytics. *Mechanisms of Ageing and Development*, *200*, 111587. https://doi.org/10.1016/j.mad.2021.111587

Zhu, Y., Doornebal, E. J., Pirtskhalava, T., Giorgadze, N., Wentworth, M., Fuhrmann-Stroissnigg, H., Niedernhofer, L. J., Robbins, P. D., Tchkonia, T., & Kirkland, J. L. (2017). New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463. *Aging (Albany NY)*, *9*, 955–963. https://doi.org/10.18632/aging.101202

Zhu, Y., Tchkonia, T., Pirtskhalava, T., Gower, A. C., Ding, H., Giorgadze, N., Palmer, A. K., Ikeno, Y., Hubbard, G. B., Lenburg, M., O'Hara, S. P., LaRusso, N. F., Miller, J. D., Roos, C. M., Verzosa, G. C., LeBrasseur, N. K., Wren, J. D., Farr, J. N., Khosla, S., Stout, M. B., McGowan, S. J., Fuhrmann-Stroissnigg, H., Gurkar, A. U., Zhao, J., Colangelo, D., Dorronsoro, A., Ling, Y. Y., Barghouthy, A. S., Navarro, D. C., Sano, T., Robbins, P. D., Niedernhofer, L. J., & Kirkland, J. L. (2015). The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*, *14*, 644–658. https://doi.org/10.1111/acel.12344