Scientific Bulletin. Series F. Biotechnologies, Vol. XXVII, No. 1, 2023
ISSN 2285-1364, CD-ROM ISSN 2285-5521, ISSN Online 2285-1372, ISSN-L 2285-1364

# METHODS TO IMPROVE BIOAVAILABILITY OF NATURAL SENOLYTICS - A MINI REVIEW

**Dana MIU, Fawzia SHAAT, Ramona-Daniela PAVALOIU**

National Institute of Pharmaceutical Chemistry R & D of Bucharest - ICCF Bucharest
112 Calea Vitan, District 3, Bucharest, Romania

Corresponding author email: pavaloiu.daniella@yahoo.com

***Abstract***

*Senolytics represent a group of substances that can eliminate senescent cells in several aging-related pathologies including Alzheimer`s disease, atherosclerosis, and type 2 diabetes, etc. Also, senolytic use has been proposed as a potential adjuvant approach to improve the response to senescence-inducing conventional and targeted cancer therapies. In various studies natural compounds (quercetin, fisetin, piperlongumine and curcumin) have been discovered to be effective senolytic agents. Despite the unequivocal promise of senolytics, some senolytics have low bioavailability. In this review, we summarize and discuss the latest methods to improve the bioavailability of immunomodulatory and/or immunostimulatory senolytic bioactive substances. Therefore, an in-depth discussion on diverse delivery strategies of senolytic agents and latest updates on a novel senotherapeutic research will be provided.*

***Key words****: bioavailability, natural compounds, senolytics.*

## INTRODUCTION

Senolytics are drugs or compounds that selectively induce the death of senescent cells, which are aged or damaged cells that no longer function correctly and can contribute to aging and age-related diseases including Alzheimer`s disease, atherosclerosis, and type 2 diabetes, etc (Van Deursen, 2014). Some natural compounds have also been shown to exhibit senolytic properties, such as: quercetin, fisetin, resveratrol, piperlongumine, curcumin, etc. The biggest challenge with natural senolytics is their low bioavailability, which refers to the amount of the compound that is absorbed and available for use in the body (Boccardi & Mecocci, 2021).

Several methods to improve the bioavailability of natural senolytics were described in literature like: i) encapsulation of natural senolytics in innovative delivery systems; ii) co-administration with absorption enhancers; iii) combination with other senolytics and iv) dose optimization.

Researchers are exploring novel delivery systems for natural senolytics, like nanoparticles or conjugating the compounds with carrier molecules that can help enhance their delivery to specific tissues or organs. These approaches hold promise for improving the bioavailability and effectiveness of natural senolytics (Obeid et al., 2017; Squillaro et al, 2018). Another strategy to improve the bioavailability of natural senolytics is to co-administration the compound with absorption enhancers, which can help improve the absorption and bioavailability of the compound (Hosseini et al., 2022).

Combining natural senolytics with other senolytic compounds, such as dasatinib or navitoclax, can also help improve their bioavailability and effectiveness, as these drugs can enhance the elimination of senescent cells and increase the overall therapeutic effect (Sierra-Ramirez et al., 2020).

Optimizing the dosage and timing of natural senolytics can also improve their bioavailability. For example, taking the compound with a high-fat meal can improve its absorption, while taking it at a specific time of day or in divided doses can help maintain optimal blood levels of the compound (Rein et al., 2013).

This review presents senolytics from natural sources and highlights the methods to improve the bioavailability of senolytic substances from natural sources. Therefore, a discussion on diverse delivery strategies of natural senolytic agents and latest updates on a novel senotherapeutic research were provided.

## MATERIALS AND METHODS

This review is based on secondary research sources. The search was carried out in various databases like ScienceDirect, Pubmed, Scopus, etc. in February 2023, using keywords like "senescence", "senescent cells", "senotherapy", "natural senolytics", "improve bioavaibility natural senolytics" and "senolytic delivery". The search was conducted taking into consideration various types of papers like reviews, books, research articles, online articles ahead of print.

## RESULTS AND DISCUSSIONS

### Senolytics from natural sources

Natural compounds that possess antioxidant and anti-inflammatory properties hold the greatest potential for promoting healthy aging and combating senescence (Gurau et al., 2018). Table 1 displays the most encouraging natural compounds for combating senescence, which have demonstrated significant reduction of senescent cells in animal models.

Table 1. Natural compounds for combating senescence

| Compounds | Target | References |
|---|---|---|
| Tocotrienols | Multiple pathways (mTOR, NFκB, miRNAs) | Lagoumtzi & Chondrogianni, 2021; Meganathan et al., 2016; |
| Quercetin | Multiple pathways (mTOR, NFκB, miRNAs) | Lagoumtzi & Chondrogianni, 2021; von Kobbe, 2019; Zhang et al, 2022; Zoico et al., 2021 |
| Curcumin | Multiple pathways (MAPK, NF-κβ, COX2, Bcl-2,cyclin B1) | Bielak-Zmijewska et al., 2019; Lagoumtzi & Chondrogianni, 2021; Li et al., 2019 |
| Resveratrol | Multiple pathways (ROS, SASP, miRNAs) | Mamun et al., 2022; von Kobbe, 2019 |
| Vitamin B3 | mTOR | Kirkland & Tchkonia, 2020; Zhang et al., 2021; Zhou, 2021 |
| Piperlongumine | Multiple pathways (ROS, apoptosis) | Lagoumtzi & Chondrogianni, 2021; Liu et al., 2018; Mamun et al., 2022 |
| Fisetin | Multiple pathways (PI3K, mTOR, SASP) | Lagoumtzi & Chondrogianni, 2021; Yousefzadeh et al., 2018 |

BCL= B-cell lymphoma 2
COX-2 = cyclooxygenase-2
MAPK = mitogen-activated protein kinases
miRNA = micro RiboNucleic Acid
mTOR = mammalian target of rapamycin
NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells
PI3K = phosphatidylinositol 3-kinase
ROS = reactive oxygen species.
SASP = senescence associated secretory phenotype

Considerable research efforts are currently focused on identifying senolytics from natural sources that may aid in the prevention of pathological conditions, particularly age-related diseases (Barrera et al., 2021; Kirkland and Tchkonia, 2020; Vázquez et al., 2022). Tocotrienols are members of the vitamin E family, which are a group of fat-soluble antioxidants that help to protect cells from oxidative damage caused by free radicals. Unlike the more well-known vitamin E form, tocopherols, tocotrienols have an unsaturated side chain that allows them to more easily penetrate cell membranes and reach deep into fatty tissues, providing enhanced antioxidant protection. They have been shown to have a range of health benefits, including anti-inflammatory and anti-cancer effects, and are being studied for their potential to prevent or treat various age-related diseases (Mecocci et al., 2018). Quercetin can targets senescent cells and triggers their programmed cell death which can help to eliminate damaged cells that might otherwise contribute to age-related diseases. At the same time, it can delay senescence and/or promote the clearance of senescent cells in healthy tissues, which can help to maintain healthy cellular function and prevent the onset of age-related diseases. This dual and complementary action makes quercetin an attractive candidate for developing senolytic therapies aimed at preventing or treating age-related diseases (Dagher et al., 2021; Geng et al., 2018; Hwang et al., 2018; Zhu et al., 2015). Fisetin (3,3′,4′,7-tetrahydroxyflavone), a flavonoid is found in strawberries, apples, persimmons, and cucumbers, has been shown to selectively induce apoptosis in senescent cells (Zhang et al., 2018; Yousefzadeh et al., 2018). Curcumin, a compound is found in turmeric, a spice commonly used in cuisine, has been shown to have anti-inflammatory and antioxidant effects, and it may also have senolytic properties (Li et al., 2019). Resveratrol, a compound found in grapes, peanuts, and red wine, has been shown to have various anti-aging effects, including the ability to modulate cell senescence (Farhadnejad et al., 2019). B3 vitamins like nicotinamide (niacinamide), niacin (nicotinic acid), and nicotinamide riboside, found in white meat, peanuts, and mushrooms, are all precursors of nicotinamide adenine dinucleotide (NAD). NAD+ is the oxidized form of NAD and serves as an essential cofactor in various cellular pathways, including energy metabolism and

oxidative stress (Sauve, 2008). Piperlongumine is a natural compound found in Piper longum, known for its anticancer properties. Research has shown that piperlongumine has a selective effect on senescent cells, inducing their cell death (Bogan & Brenner, 2008; Wang et al., 2016; Zhang et al., 2018).

**Methods to improve the bioavailability of natural senolytics**

***Encapsulation of senolytics in innovative delivery systems***

The use of nanotechnology in natural senolytics delivery is an emerging field that shows great promise in improving the effectiveness and reducing the side effects of senolytic therapies (Squillaro et al., 2018). Nanotechnology offers several advantages in senolytic drug delivery, such as targeted delivery, controlled release, and increased cellular uptake. By designing nanocarriers with specific properties, such as size, shape, and surface charge, the delivery of senolytics can be targeted to senescent cells while minimizing damage to healthy cells. Moreover, nanocarriers can encapsulate senolytics, protecting them from degradation and enhancing their bioavailability (Obeid et al., 2017). Additionally, smart nanocarriers can be designed to release senolytics in response to specific signals or 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).

The initial innovative nanosystem that was developed to deliver cargo specifically to senescent cells is a mesoporous silica nanoparticle structure coated with galacto-oligosaccharides and loaded with rhodamine B, in which the nanoparticles are taken up by human senescent cells, they become activated by SA-β-gal (Agostini et al., 2012). Additionally, research has demonstrated that encapsulating a senolytic agent, navitoclax, with β (1,4)-galacto-oligosaccharides effectively removes senescent cells in models of senescence induced by damage or chemotherapy (Muñoz-Espín et al. 2018). Conjugating drugs with nanostructures can also potentially exhibit a senomorphic effect by blocking the SASP (Thapa et al., 2017; Lewinska et al., 2020). An *in vitro* study conducted recently found that nanoparticles modified with a monoclonal antibody against the CD9 receptor (which is overexpressed in aging cells) and loaded with rapamycin (a well-known mTOR inhibitor with anti-aging properties) can exhibit an anti-senescence effect (Thapa et al., 2017). Additionally, promising results have been documented for CD9-targeted PEGylated liposomes as a drug delivery system to target senescent cells. The uptake of these liposomes was found to be higher in premature senescent human dermal fibroblasts compared to young human dermal fibroblasts (Nguyen et al., 2017). Furthermore, there has been research conducted to explore the targeted delivery of rapamycin (known as a senolytic) to decrease senescence in cells that overexpress the CD9 receptor. Results indicated that rapamycin promoted cell proliferation and reduced the number of SA-β-gal-positive cells (Nguyen et al., 2017). Ke et al. (2018) showed that MoS2 NPs suppressed hydrogen-peroxide-induced senescence in endothelial cells.

All of these systems were proven effective for the delivery various senolitic substances, and could be explored for senolytics from natural sources. Furthermore, research has demonstrated that magnetite nanoparticles functionalized with quercetin (known as MNPQ) exhibit both senolytic and senostatic activity in prematurely-senescent human fibroblasts (via hydrogen peroxide treatment *in vitro*). *In vitro* experiments showed that MNPQ particles were able to eliminate senescent human fibroblast cells. MNPQ was also found to decrease the senescence-mediated proinflammatory response, as evidenced by reduced secretion of IL-8 and IFN-β, accompanied by the activation of AMP-activated protein kinase (Lewinska et al., 2020). Other innovative delivery systems include nanosuspensions, dendrimers, carbon nanotubes, polymeric micelles and lipid based nanoparticles such as liposomes, solid lipid nanoparticle, nanoemulsion and nanostructured lipid carriers are extensively reported to enhance the solubility, bioavailability of resveratrol, curcumin, quercetin, epigallocat echin gallate (EGCG), and fisetin, but were not yet explored for senotherapy (Nagesh et al.,

2019; Obeid et al., 2017; Squillaro et al., 2018). Overall, the use of nanotechnology in senolytic drug delivery holds tremendous potential in improving the efficacy and safety of senolytic therapies and could pave the way for new treatments for ageing and age-related diseases.

***Co-administration with absorption enhancers***

Co-administration of natural senolytics with absorption enhancers has been proposed as a potential strategy to improve the bioavailability and efficacy of these compounds. Absorption enhancers are compounds that increase the absorption of other substances across biological membranes. Studies have shown that absorption enhancers can increase the bioavailability and pharmacological activity of natural senolytics (Hosseini et al., 2022). For example, the natural senolytic fisetin has low bioavailability due to its limited absorption and rapid elimination from the body. However, co-administration of fisetin with quercitin has been shown to increase its bioavailability (Hosseini et al., 2022), that has the potential to improved efficacy in eliminating senescent cells. Similarly, another study showed that co-administration of the natural senolytic quercetin with the absorption enhancer piperine increased the bioavailability and therapeutic effects of quercetin in age-related diseases (Sharma et al., 2020). Therefore, co-administration of natural senolytics with absorption enhancers has the potential to be a promising approach to improve the efficacy of natural senolytics in eliminating senescent cells,

***Combination with other senolytics***

The combination of natural senolytics with other senolytics is an emerging strategy to increase the effectiveness of senotherapy in the treatment of age-related diseases.

Studies have shown that combining natural senolytics with other senolytics can increase their senolytic activity and improve their therapeutic effects. For example, the combination of the natural senolytic fisetin with the senolytic dasatinib has been shown to improve the clearance of senescent cells in vitro and in vivo, resulting in improved healthspan and lifespan in animal models of age-related diseases (Colman et al., 2020). Similarly, the combination of the natural senolytic quercetin with the senolytic navitoclax has been shown to have synergistic effects in eliminating senescent cells and improving the healthspan in mouse models of age-related diseases (Sierra-Ramirez et al., 2020). The combination of senolytic dasatinib and quercetin has been extensively studied and has been shown to eliminate senescent cells in both human and animal models (Xu et al, 2018; Zhu et al., 2015). While the combination of dasatinib and quercetin is not FDA-approved for this indication at the present, it has been tested/proposed in several clinical trials for the treatment of various age-related diseases, such as frailty, mild cognitive impairment and Alzheimer's disease (Boccardi & Mecocci, 2021). Overall, combining natural senolytics with other senolytics may represent a suitable approach for enhancing the effectiveness of senotherapics in the treatment of age-related diseases. However, more research is needed to optimize the dosages and combinations of natural senolytics and other senolytics, as well as to assess their safety and potential side effects.

**Dose optimization**

Optimizing the dosage and timing of natural senolytics is an important consideration for improving bioavailability and efficacy of natural senolytics. There are several factors to consider when determining the optimal dosage and timing of natural senolytics. One factor is absorption, which can be affected by factors such as food intake. For example, some natural senolytics have poor solubility and limited bioavailability, which can be improved by taking them with a high-fat meal. The presence of fat in the meal can increase the absorption of these compounds by enhancing their solubility and uptake in the intestines (Rein et al., 2013). Another factor is the timing of administration, which can influence the pharmacokinetics and bioavailability of the compound. For example, some natural senolytics have a short half-life and may require frequent dosing to maintain effective blood levels. Therefore, optimizing the dosage and timing of natural senolytics can improve their bioavailability and therapeutic effects, and may have important clinical implications for the treatment of age-related diseases. However, it is important to note that

the optimal dosages and timing of natural senolytics may vary depending on the specific compound, individual patient factors, and the disease being treated, and should be determined on a case-by-case basis (Rein et al., 2013).

## CONCLUSIONS

This review presents senolytics from natural sources and highlights the methods to improve their bioavailability like encapsulation in innovative delivery systems, co-administration with absorption enhancers, combination with other senolytics and dose optimization. Overall, these methods have shown promise in improving the bioavailability of natural senolytics, which could lead to enhanced therapeutic efficacy and improved health outcomes.

## ACKNOWLEDGEMENTS

This work was carried out through the “Nucleu” Program, Contract no. 1N/2023, Project code PN 23-28 - "Advanced multidisciplinary researches for the identification and characterization of alternative innovative products and technologies, applicable in the life sciences, BioChemLife", within the National Plan for Research and Development and Innovation 2022-2027, carried out with the support of MCID, project no. PN 23-28 03 01.

## REFERENCES

Adamczyk-Grochala, J., & Lewinska, A. (2020). Nano-Based Theranostic Tools for the Detection and Elimination of Senescent Cells. *Cells*, *9(12)*, 2659.

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. *Angewande Chemie International Edition*, *51*, 10556–10560.

Barrera, V.O.S.; Gómez, V.J.C.; Magos, G.G.A. (2021). Chemoinformatic screening for the selection of potential senolytic compounds from natural products. *Biomolecules*, *11(3)*, 467.

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.

Boccardi, V., Mecocci, P. (2021). Senotherapeutics: Targeting senescent cells for the main age-related diseases. *Mechanisms of ageing and development*, *197*, 111526.

Bogan, K.L., Brenner, C. (2008). Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD+ precursor vitamins in human nutrition. *Annuar Review of Nutrition, 28*, 115–130.

Colman, R., Tchkonia, T., Pirtskhalava, T., Giorgadze, N., Prata, L., Schaefer, K., Kirkland, J. (2020). Effect of Combined Dasatinib and Fisetin Treatment on Senescent Cell Clearance in Monkeys. *Innovation in Aging*, *4(1)*, 131–132.

Dagher, O., Mury, P., Thorin-Trescases, N., Noly, P.E., Thorin, E., Carrier, M. (2021). Therapeutic potential of quercetin to alleviate endothelial dysfunction in age-related cardiovascular diseases. *Frontiers in Cardiovascular Medicine*, 8, 220.

Farhadnejad, H., Emamat, H., Zand, H. (2019). The Effect of Resveratrol on Cellular Senescence in Normal and Cancer Cells: Focusing on Cancer and Age-Related Diseases. *Nutrition and cancer*, *71(7)*, 1175–1180.

Geng, L., Liu, Z., Zhang, W., Li, W., Wu, Z., Wang, W., Ren, R., Su, Y., Wang, P., Sun, L., Ju, Z., Chan, P., Song, M., Qu, J., Liu, G.-H. (2018). Chemical screen identifies a geroprotective role of quercetin in premature aging. *Protein Cell, 10(6)*, 417-435.

Gurau, F., Baldoni, S., Prattichizzo, F., Espinosa, E., Amenta, F., Procopio, A.D., Albertini, M.C., Bonafˋe, M., Olivieri, F. (2018). Anti-senescence compounds: a potential nutraceutical approach to healthy. *Ageing Research Reviews, 46*, 14-31.

Hwang, H.V., Tran, D.T., Rebuffatti, M.N., Li, C.-S., Knowlton, A.A. (2018). Investigation ofquercetin and hyperoside as senolytics in adult human endothelial cells. *PLoS One*, 13, e0190374.

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.

Kirkland, J.L., Tchkonia, T. (2020). Senolytic drugs: From discovery to translation. *Journal of Internal Medicine*, *288(5)*, 518-536.

Lagoumtzi, S. M., & Chondrogianni, N. (2021). Senolytics and senomorphics: Natural and synthetic therapeutics in the treatment of aging and chronic diseases. *Free radical biology & medicine*, *171*, 169–190.

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.

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 Fe3O4 nanoparticles during oxidant-induced senescence in human fibroblasts. *Redox Biology*, *28*, 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.

Liu, X., Wang, Y., Zhang, X., Gao, Z., Zhang, S., Shi, P., Zhang, X., Song, L., Hendrickson, H., Zhou, D., & Zheng, G. (2018). Senolytic activity of piperlongumine analogues: Synthesis and biological evaluation. *Bioorganic & medicinal chemistry*, *26(14)*, 3925–3938.

Mamun, A. A., Sufian, M. A., Uddin, M. S., Sumsuzzman, D. M., Jeandet, P., Islam, M. S., Zhang, H. J., Kong, A. N., & Sarwar, M. S. (2022). Exploring the role of senescence inducers and senotherapeutics as targets for anticancer natural products. *European journal of pharmacology*, *928*, 174991.

Mecocci, P., Boccardi, V., Cecchetti, R., Bastiani, P., Scamosci, M., Ruggiero, C., Baroni, M. (2018). A long journey into aging, brain aging, and Alzheimer's disease following the oxidative stress tracks. *Journal of Alzheimer's Disease*, *62*, 1319–1335.

Meganathan, P., & Fu, J. Y. (2016). Biological Properties of Tocotrienols: Evidence in Human Studies. *International journal of molecular sciences*, *17(11)*, 1682.

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.

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.

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.

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.

Rein, M. J., Renouf, M., Cruz-Hernandez, C., Actis-Goretta, L., Thakkar, S. K., & da Silva Pinto, M. (2013). Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *British journal of clinical pharmacology*, *75(3)*, 588–602.

Sauve, A. (2008). NAD+ and Vitamin B3: From Metabolism to Therapies. *Journal of Pharmacology and Experimental Therapeutics*, *324 (3)*, 883-893.

Sierra-Ramirez, A., López-Aceituno, J.L., Costa-Machado, L.F., Plaza, A., Barradas, M., Fernandez-Marcos, P.J. (2020). Transient metabolic improvement in obese mice treated with navitoclax or dasatinib/quercetin. *Aging*, *12(12)*, 11337–11348.

Hosseini, S.S., Ebrahimi, S.O., Ghasem Kashani, M.J., Reiisi, S. (2023). Study of quercetin and fisetin synergistic effect on breast cancer and potentially involved signaling pathways. *Cell Biology International*, *47(1)*, 98-109.

Sharma, S, Raj, K, Singh, S. (2020). Neuroprotective effect of quercetin in combination with piperine against rotenone-and iron supplement-induced parkinson's disease in experimental rats. *Neurotoxicity Research*, *37(1)*, 198–209.

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.

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.

Van Deursen, J.M. (2014). The role of senescent cells in ageing. *Nature*, *509 (7501)*, 439-446.

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.

von Kobbe C. (2019). Targeting senescent cells: approaches, opportunities, challenges. *Aging*, *11*(24), 12844–12861.

Wang, Y., Chang, J., Liu, X., Zhang, Xuan, Zhang, S., Zhang, Xin, Zhou, D., Zheng, G. (2016). Discovery of piperlongumine as a potential novel lead for the development of senolytic agents. *Aging (Albany NY)*, 8, 2915.

Xu, M., Pirtskhalava, T., Farr, J. N., Weigand, B. M., Palmer, A. K., Weivoda, M. M., Inman, C. L., Ogrodnik, M. B., Hachfeld, C. M., Fraser, D. G., Onken, J. L., Johnson, K. O., Verzosa, G. C., Langhi, L. G. P., Weigl, M., Giorgadze, N., LeBrasseur, N. K., Miller, J. D., Jurk, D., Singh, R. J., Kirkland, J. L. (2018). Senolytics improve physical function and increase lifespan in old age. *Nature medicine*, *24(8)*, 1246–1256.

Zhang, Q., Li, S., Chen, F., Zeng, R., & Tong, R. (2022). Targeted delivery strategy: A beneficial partner for emerging senotherapy. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *155*, 113737.

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.

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.

Zhang, P., Kishimoto, Y., Grammatikakis, I., Gottimukkala, K., Cutler, R.G., Zhang, S., Abdelmohsen, K., Bohr, V.A., Misra Sen, J., Gorospe, M., Mattson, M.P. (2019). Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an 'Alzheimer's disease model. *Nature Neuroscience, 22*, 719–728.

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.

Zhou F. Q. (2021). $NAD^+$, Senolytics, or Pyruvate for Healthy Aging?. *Nutrition and metabolic insights*, *14*, 11786388211053407.

Zoico, E., Nori, N., Darra, E. *(2021)* Senolytic effects of quercetin in an in vitro model of pre-adipocytes and adipocytes induced senescence. *Scientific Reports Nature* 11, 23237.