Journal of Young Pharmacists, 2026; 18(2):300-309.
https://www.jyoungpharm.org

Review Article

Pharmacological Targeting of Cellular Senescence: Molecular Mechanism and Anti-Ageing Strategies in Chronic Diseases Pathophysiology

Sekhar Sharma[1,*], Bhumika Chettri[2], R Keerthi Shree[1], Namana G[1], Rakshitha N P[1], Benson Babu Thomas[1], Sreya Krishna B[1], Suryan V V[1], Rajendra Dhakal[1]

[1]Department of Pharmacy Practice, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, INDIA.
[2]Department of Pharmacognosy and Phytochemistry, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, INDIA.

ABSTRACT

Cellular senescence is a condition in which cells permanently stop dividing due to factors such as DNA damage, telomere shortening, oxidative stress, and mitochondrial dysfunction. Initially, this process is considered protective because it prevents damaged cells from becoming cancerous. However, with increasing age, senescent cells accumulate in the body and contribute to various health problems. These cells secrete inflammatory factors known as senescence-associated secretory phenotypes (SASP), which promote chronic inflammation and may contribute to the development of age-related conditions. This review aims to summarize the molecular mechanisms and chemistry of cellular senescence, its role in chronic diseases, and the pharmacological approaches involving senolytic drugs. Various papers were searched using Google Scholar and PubMed for senolytic, cellular senescence, dasatinib, quercetin, fisetin, rapamycin, navitoclax, the mechanism of senescence, chemistry, and clinical trials involved in this topic. This review discusses the molecular mechanism of cellular senescence, chemistry its role in chronic diseases, and also current pharmacologic approaches. Targeting cellular senescent shows a promising therapeutic strategy, however further studies are required to established long term safety, efficacy and clinical translation.

Keywords: Cellular Senescence, Chronic Diseases, Dasatinib, Quercetin, SASP, Senolytic.

Correspondence:
Sekhar Sharma
Department of Pharmacy Practice,
Krupanidhi College of Pharmacy,
Bengaluru-560035, Karnataka, INDIA.
Email: drsharmasekhar54321@gmail.com

Received: 16-01-2026;
Revised: 05-03-2026;
Accepted: 24-04-2026.

INTRODUCTION

Cellular senescence is a fundamental stress response mechanism that is characterized by stable cell cycle arrest, prevents proliferation of the damaged cell, and promotes tissue repair through a paracrine signaling mechanism (Herranz *et al*., 2018). It gets triggered by telomere attrition, oncogenic stress, or persistent DNA damage, which includes reactive oxygen species-induced chemicals like 8-oxyguanine (Ray *et al*., 2025). Senescent cells will accumulate with age, which secretes Senescence-Associated Secretory Phenotype (SASP) (Han *et al*., 2022). SASP causes activation of inflammatory cytokines like IL-6, IL-8, chemokinesis, and matrix metalloproteinase, driving chronic low-grade inflammation that will contribute to the pathophysiology of chronic diseases such as atherosclerosis, type 2 diabetes, and neurodegenerative disorders (Ohtani *et al*., 2022; Cuollo *et al*., 2020).

Pharmacological targeting of the senescent cell through senolytic agents, which induce apoptosis in these cells, has been a promising step for anti-aging strategy (Saliev *et al*., 2025). First-generation senolytic agents such as dasatinib and quercetin disrupt networks such as the BCL-2 family protein and the P13K/AKT pathway, which is evident in preclinical models of age-related pathologies (Richardson *et al*., 2024). SAR of dasatinib and quercetin explains the senolytic action of dasatinib's competitive binding to the Src kinase ATP pocket with high affinity (Kd=0.4*n*M), blocking the signal through the quinazoline-thiazole structure, while quercetin's planar flavonoid rings form hydrogen bonds with HSP90, disrupting the chaperone protection differently (Alharbi *et al*., 2022).

In chronic diseases, senescent cells proliferate excessively in the tissues, which worsens the chronic condition (Kirkland *et al*., 2017). Senescent cell burden is related to endothelial dysfunction in cardiovascular diseases and beta cell failure in diabetes, where SASP will cause insulin resistance through NF-kB activation (Narasimhan *et al*., 2021; Mahoney *et al*., 2025). A recent trial showed that the (D+Q) dasatinib and quercetin combination

DOI: 10.5530/jyp.20260026

showed reduced fibrosis and better glycemic control (Ruggiero *et al.*, 2025). This review focuses on how senescence starts, analyzes the SAR of senolytic drugs, and explores the real-world application. It also highlights the pharmacy innovation drug design for better targeting. It also addresses the gap in precision senotherapeutics for India's rising chronic disease burden, which has the highest number of diabetes and heart diseases worldwide.

MOLECULAR PATHWAY

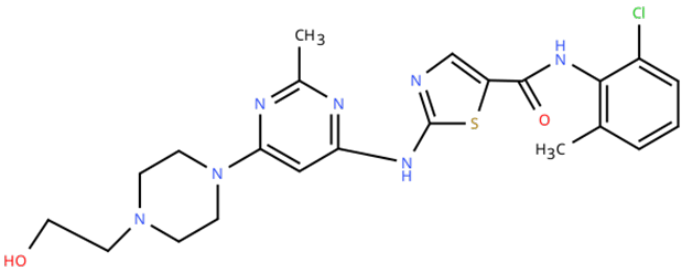
Molecular pathways in cellular senescence will trigger stress responses, integrate DNA damage signaling and epigenetic reprogramming, and alter cell metabolism, this process causes diseases like atherosclerosis (Shmulevich *et al.*, 2020). In the DNA Damage Response (DDR), where the double strands break in DNA, it acts as an alarm. They will activate ATM and ATR kinase enzymes that sense damage. The ATM will focus on the double-strand break, while the ATR will address single- strand issues during the replication process (Xiong *et al.*, 2022). This kinase will then add a phosphate group, i.e., phosphorylate CHK1 and CHK2 checkpoint kinases. This chain reaction will stabilize the p53 tumor suppression protein, which turns on p21^CIP1. It stops the cell cycle at G1/ S, preventing the damaged DNA (Smith *et al.*, 2020).

The p16^INK4a level will rise, which blocks the CDK4/6 enzyme, which phosphorylates retinoblastoma protein. Whereas unphosphorylated RB will stay active, which causes binding of E2F transcription factors and will disrupt the gene needed for DNA synthesis (Wagner *et al.*, 2020). In atherosclerosis this pathway causes plaque buildup as senescent cells inflame in this area. Persistent DNA damage response will make the stress signal active, which causes SAHF (Shah *et al.*, 2015). This happens through HP1v protein binding and H3K9me3 chemical tags. Cells energize SA-β-gal, a detectable enzyme marker, because autophagy fails, which causes the buildup of waste at low pH. NF-κB and C/EBPβ transcription factors will get activated due to the IL-1a autocrine loop (Alexandru *et al.*, 2025). This pumps out IL-6/IL cytokines, which will cause inflammation to the nearby cells, further damaging the diabetic beta cells or neurons in neurodegeneration. The NAD+ energy will also drop, which then disables SIRT1 (sirtuin deacetylase), which stops the SASP secretion through unchecked NF-kB activity (Kauppinen *et al.*, 2013). A pharmacological study reveals how chemical properties of senolytics cause weakness in the senescent cell survival pathway. Dasatinib and the quinazoline structure will block the Src and FAK kinase by fitting into the ATP binding, the aromatic ring will get stacked up with the positive charge residue, thus breaking the signal that keeps the senescent alive (Wilson *et al.*, 2014). Quercetin will attack the BCL2 protein and HSP90 by forming a hydrogen bond through the catechol hydroxyl group. The SAR shows that adding the methoxyl group at the C-3 position will prevent all the unwanted effects in chronic diseases, the pathways will overlap and will amplify the senescence (Iacopetta *et al.*, 2017).

Senolytic Drug Chemistry

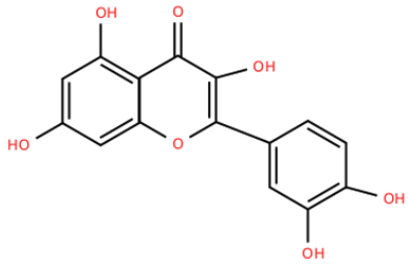
The senolytic drug basically acts on small molecules that will cause apoptosis in senescent cells; they work by targeting the anti-apoptosis pathway, like BCL-2 family protein and pro-survival kinase (Basu, 2025). Many of these agents are taken from cancer treatment, i.e., they are repurposed through chemistry tests and SAR studies to fit and attack only the senescent cell. Examples include dasatinib, quercetin, fisetin, and navitoclax. Their chemical makeup makes them easy to penetrate inside the cell (Richardson *et al.*, 2024).

Dasatinib ($C_{22}H_{26}$ ClN_7O_2S) is a thiazole-based tyrosine kinase inhibitor. It targets the SRC and BCR ABL kinase upregulated in senescent cells, blocking the FAK and PI3K/AKT. Its structure is tweaked to make it more lipophilic, making lysosomal accumulate in senescent cells with high beta- galactosidase activity (Agustín *et al.*, 2023; Das *et al.*, 2006).



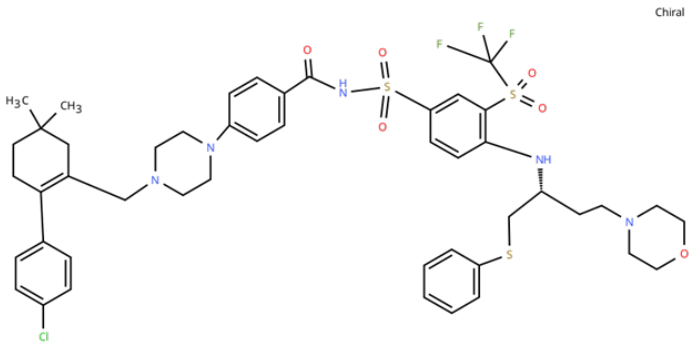
Dasatinib Chemical Structure

Quercetin ($C_{15}H_{14}O_7$), a flavonol, inhibits BCL-2 and will reduce SASP via NF-κB suppression. Forms like rutin help it absorb in the body better. Together the combination of dasatinib and quercetin is used to kill senescent cells by attacking different paths at once (Fan *et al.*, 2022).



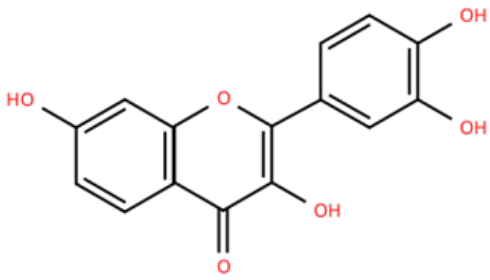
Quercetin Chemical Structure

Navitoclax (ABT-236, $C_{30}H_{25}ClN_6O_5$) is an indole molecule that acts as a BH3 mimetic agent; it basically mimics the natural BH3 protein to block the BCL-2, BCL-xL, and BCL-W proteins. This causes the BAX protein to attack the mitochondria, which then causes apoptosis. The presence of a chlorophenyl group and sulfonamide creates high power for binding but causes thrombocytopenia (Walensky *et al.*, 2011).



Navitoclax Chemical Structure

Fisetin ($C_{15}H_{10}O_6$), a flavonol with a 3,3',4',7-tetrahydroxyflavone structure, will turn on the AMPK and SIRT1 enzymes through its 7-hydroxy group, which causes autophagy and helps control harmful reactive oxygen species (Yen *et al.*, 2017).



Fiestin Chemical Structure

In the docking studies the FOXO4-DRI peptide will break the FOXO-p53 protein interaction, whereas the HSP90 blocker, like Tanespimycin, uses a geldanamycin structure, which destabilizes the senescent cell protein (Bourgeois *et al.*, 2025). Rapamycin, a macrolide, blocks the mTORC1 at a nonactive site, which slows the senescence (Blagosklonny, 2022). The improved version of it, called Everolimus, offers better targeting (Wall *et al.*, 2012). Natural compounds like curcumin and resveratrol tweak the p53 and NF-kB pathways, but they are poorly absorbed and are now linked to nanoparticles for better delivery (Vaiserman *et al.*, 2020). In an animal study, D+Q and fisetin eases brain decline by clearing the inflammatory factors like SASP (Garbarino *et al.*, 2020). A clinical trial confirms D+Q blood level peaks at 1-2 ug/mL in lung fibrosis, proving real-world feasibility (Nambiar *et al.*, 2023).

Targeting Senescence in Chronic Diseases

Senescence plays a very important role in the pathophysiology of various diseases, including cardiovascular diseases, diabetes, neurodegeneration and idiopathic pulmonary diseases, osteoarthritis, chronic kidney diseases, type 2 diabetes mellitus, cancer therapy-induced senescence, and chronic obstructive pulmonary diseases (Zheng *et al.*, 2024). Senescence will selectively eliminate the SnCs that show disease-specific efficacy, largely seen in animal models, with emerging early-phase human data. But the efficacy also depends upon the cell type, tissue context, and senolytic class (Chen *et al.*, 2024).

Idiopathic Pulmonary Fibrosis

In murine IPF models we could see that Dasatinib and Quercetin (D+Q) reduced senescent alveolar epithelial cells and decreased fibrosis with improved lung compliance. The genetic clearance

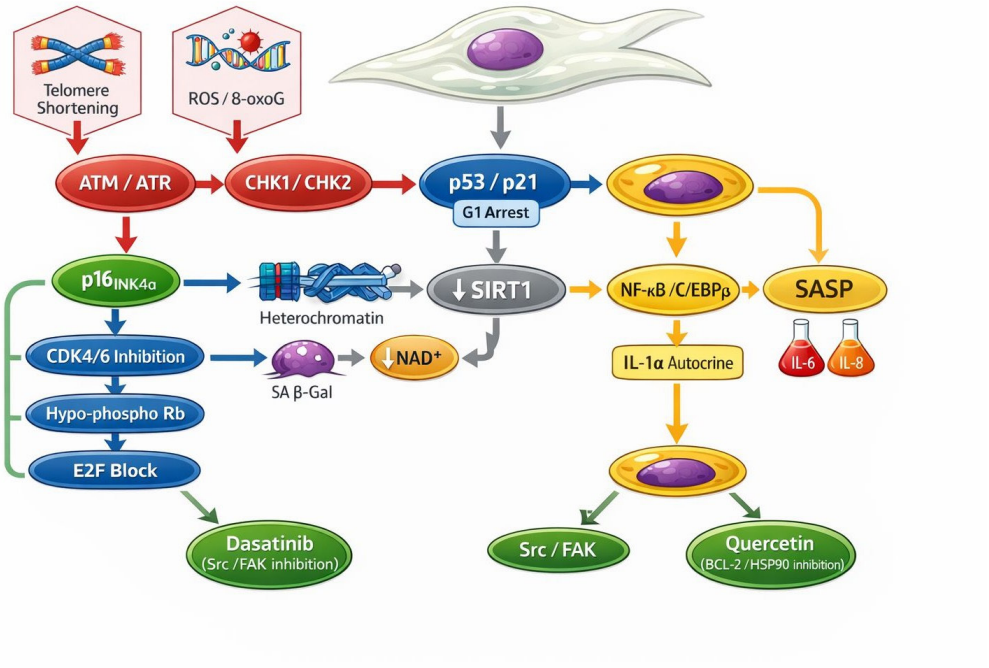


Figure 1: Senescence pathways integrating DDR (p53/p21), Rb axis, metabolic shifts (NAD+/SA- β-gal), and SASP; Senolytics target enriched vulnerabilities.

Table 1: Disease- Specific Senolytic Efficacy in Chronic Disorder.

Disease	Senescent Cell Type	Senolytic Agent	Model	Outcome	Translational Stage	References
Idiopathic Pulmonary fibrosis	Alveolar Epithelial Cells, Fibroblast	Dasatinib and Quercetin	Bleomycin Mouse Model	Decrease Fibrosis	Preclinical + Phase I pilot	(Schafer *et al.*, 2017)
Atherosclerosis	Vascular Smooth Muscles	Navitoclax, Dasatinib and Quercetin	Aged mouse	Decrease Plague burden	Preclinical	(Suda *et al.*, 2023)
Osteoarthritis	Senescent Chondrocytes	Navitoclax	Post traumatic OA mouse model	Decreases Cartilage Degeneration	Preclinical	(Larbie *et al.*, 2024)
Chronic Kidney Diseases	Tubular Epithelial Cells	Dasatinib and Quercetin	UUO model	Decreases Renal Fibrosis	Preclinical	(Li *et al.*, 2025)
Type 2 Diabetes Mellitus	Beta Cells	Dasatinib and Quercetin	Aged and Obese mouse	Improved Glucose Tolerance and increase insulin sensitivity	Preclinical	(Is *et al.*, 2023)
Alzheimers Diseases	Senescent Astrocytes Microglia	Navitoclax and Fiestin	Tau Transgenic Mouse Model	Decreases Tau Pathology	Preclinical	(Ng PY *et al.*, 2024)
Cancer Therapy Induced Senescence	Therapy induced Senescent tumor cells	BCL-XL inhibitors	Chemotherapy mouse model	Decreases Tumor Recurrence	Preclinical	(Saleh *et al.*, 2020)
COPD	Airway Epithelial cell	Dasatinib and Quercetin	Cigarette Smoke mouse model	Decreases SASP	Preclinical	(Bake *et al.*, 2025)

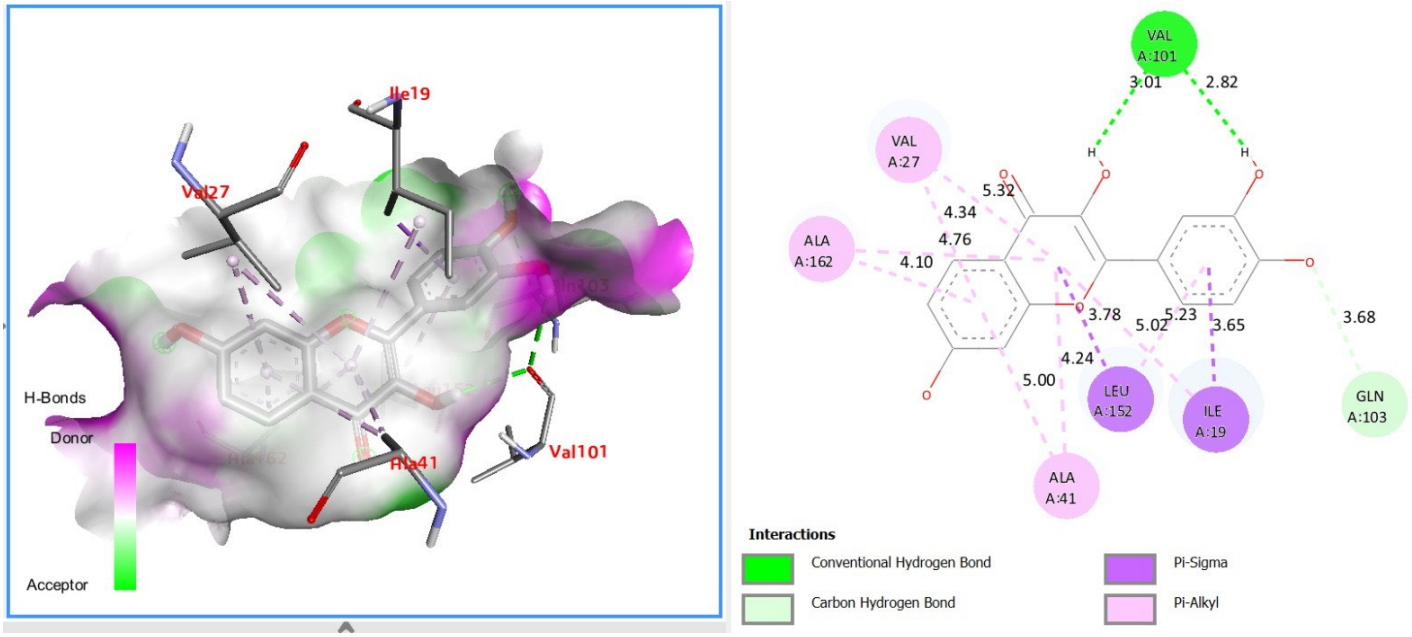


Figure 2: Quercetin docking in NF-κB p50 subunit with nanoparticle-enhanced interactions for SASP suppression.

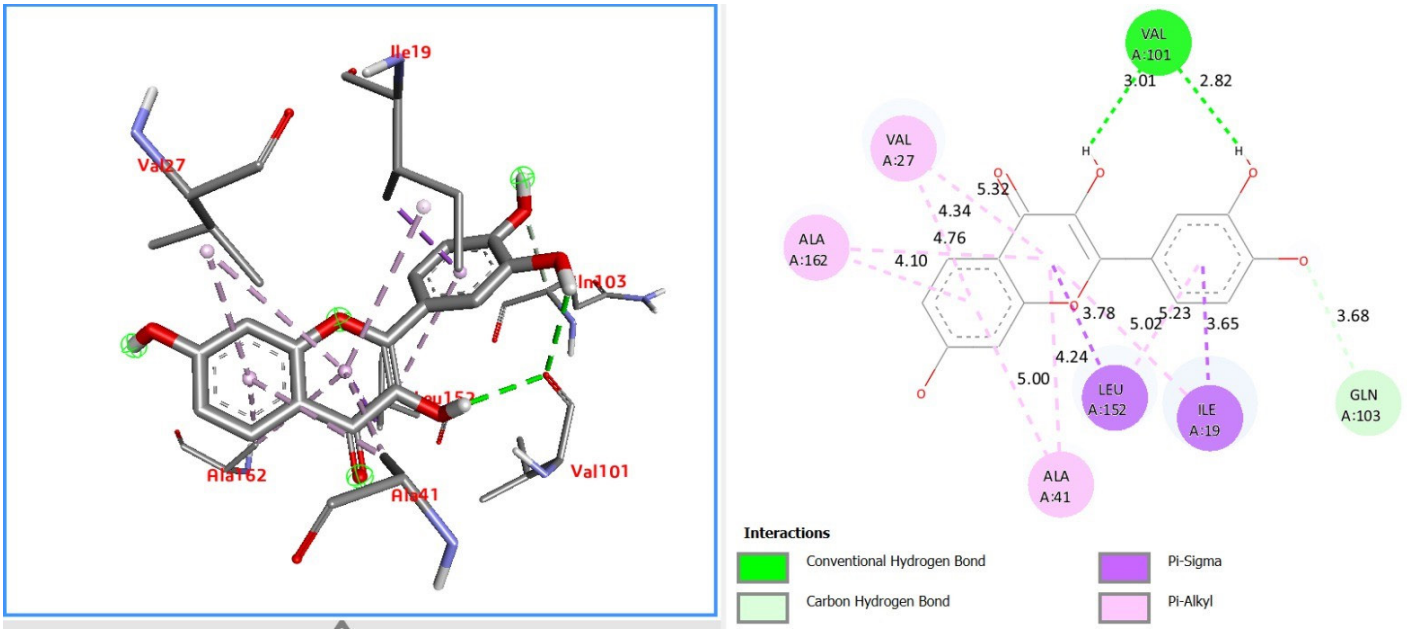


Figure 3: Dasatinib docking in NF-κB p50 active site for SASP suppression. 3D pose with H-bonds; (B) 2D interactions (green: H-bonds 2.5-3.5Å; purple: π-contacts). D+Q clinical Cmax 1 µg/mL.

of a senescent cell that is p16^ink4a was found to reduce the progression of diseases, which shows that this plays an important role in pathological conditions. When we eliminate these senescent cells, the tissue function improves. A first human pilot study showed improved physical function and mobility (Schafer *et al*., 2017).

Cardiovascular Diseases

The preclinical study also supports the efficacy of senolytic therapy in cardiovascular diseases. Senescent endothelial cells and vascular smooth muscle play a very important role in atherosclerotic plaque and vascular dysfunction. In animal models, when Navitoclax and the combination of Dasatinib and Quercetin were given, they showed a reduction in atherosclerosis and also showed there was a significant improvement in endothelial function and normal vasodilation in aged hyperlipidemic mice. Furthermore, it also decreased the levels of pro-inflammatory components of SASP (Senescence-Associated Secretory Phenotype), including a decrease in interleukin-6 and Monocyte Chemoattractant Protein MCP-1 (Suda *et al*., 2023).

Osteoarthritis

There is also strong evidence in support of senolytic therapy in osteoarthritis. In preclinical models the intra-articular clearance of senescent showed a significant reduction in cartilage degeneration. A senolytic agent helps preserve the joint structure and will also effectively suppress the inflammation through SASP. This result showed a promising therapeutic strategy, as it allowed the elimination of the senescent cell within the joint while minimizing the toxicity (Larbie *et al*., 2024).

Chronic Kidney Diseases

A preclinical study shows that the senolytic therapy has disease-modifying effects in renal disorders. Renal tubular cell senescence is the main reason for the development of fibrosis and significant loss of kidney function. in the experimental. model of CKD and diabetic nephropathy, senolytic treatment will decrease the senescent cells, preventing the interstitial fibrosis and also improving the renal function; this decreases the activation of the profibrotic pathway and also reduces the inflammatory signaling (Li *et al*., 2025).

Type 2 Diabetes Mellitus

We could also see that senolytic therapy shows a specific metabolic benefit. Senescent pancreatic beta cells will impair the insulin secretion and will disregard the glucose homeostasis. By targeting and eliminating this senescent, it shows improved glucose tolerance and increased insulin sensitivity in aged and obese mouse models. Clearing the senescent cell in adipose tissue will also cause a reduction in systemic inflammation. This study shows that the selective targeting of senescent cells shows a distinct therapeutic benefit. Dasatinib and quercetin are the key senolytic agents involved in this effect (Islam *et al*., 2023).

Neurodegenerative Diseases

Preclinical study also shows that senolytic therapy can cause both cognitive and pathological improvement in neurodegenerative diseases. Senescent astrocytes and microglia will cause chronic neuroinflammation and neuronal damage. In a transgenic model of Alzheimer's, senolytic clearance of the senescent glial cell caused a reduction in tau pathology and also decreased neuroinflammation with improved cognitive performance. Key

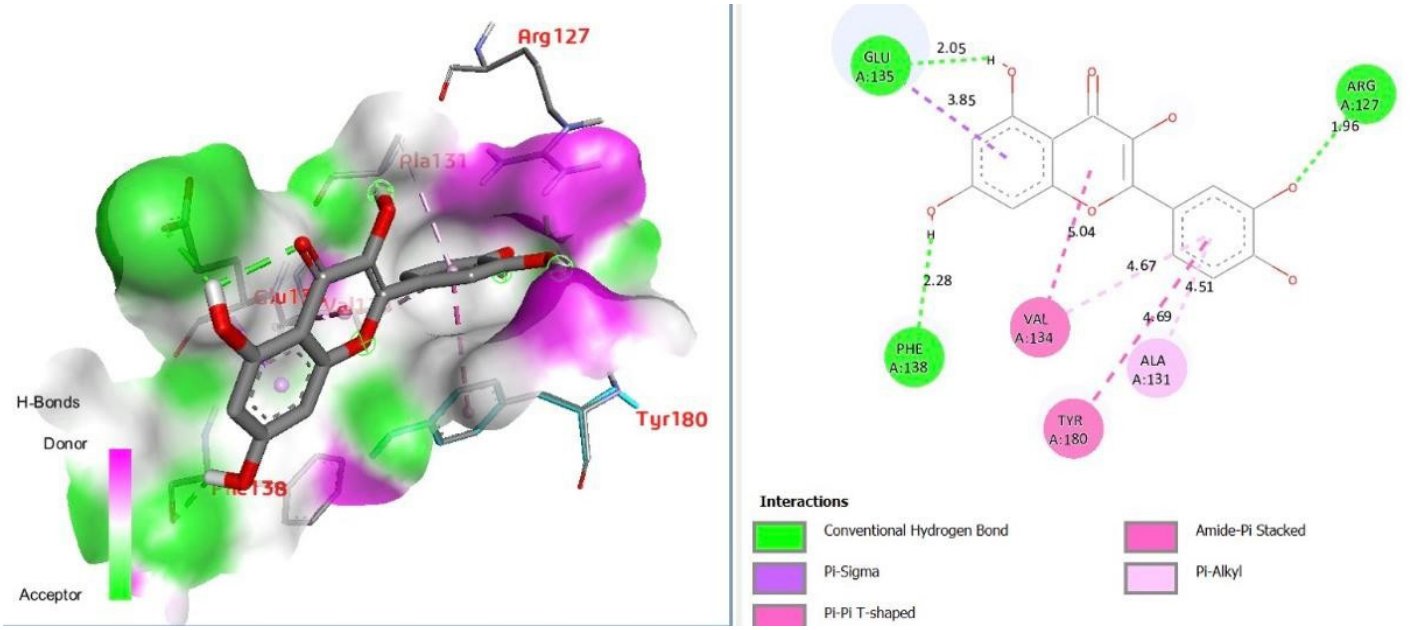


Figure 4: Fisetin docking in NF-κB p50 active site for SASP suppression. 3D pose with H-bonds; (B) 2D interactions (green: H-bonds 2.5-3.5Å; purple: π-contacts). Complements D+Q clinical profile.

senolytic agents that are associated with these effects include Navitoclax and fisetin (Ng PY *et al.*, 2024).

Cancer Therapy-Induced Senescence

Chemotherapy induced cellular senescence in the tumor cell and surrounding stromal microenvironment, which promotes tumor relapse through the pro-tumorigenic action of the SASP. In some studies, we saw the use of a senolytic agent enhance tumor control by eliminating the senescent cell. However, in another model, senolytic treatment has worsened the outcome. This finding shows the importance of the disease's context, treatment timing, and cellular targets. The key agent used in the study includes BCL-XL inhibitors (Saleh *et al.*, 2020).

Chronic Obstructive Pulmonary Diseases

Evidence also shows an important role of senolytic therapy in chronic obstructive pulmonary disease. Senescent epithelial and immune cells will contribute to persistent airway inflammation and lung dysfunction. In the smoke-exposed mouse model, we could see that senolytic approaches would reduce the SASP, which results in measurable improvement in lung mechanics. Dasatinib and quercetin are the semigraphic compounds used (Baker, *et al.*, 2025).

Preclinical and Clinical Evidence

Senolytic drugs are designed to remove senescent cells, which are damaged cells that accumulate with age and contribute to chronic diseases. The most important advantage of these drugs is based upon a hit-and-run dosing strategy because senescent cells do not rapidly reaccumulate; treatment can be given intermittently, reducing the toxicity (Kirkland *et al.*, 2020).

In an animal model, senolytics show a strong effect across tissues. Dasatinib and quercetin, clear approximately 50 to 70% of senescent cells (Islam *et al.*, 2023). When the study was done on aged mice, D=Q extended the median life span and also reduced the frailty index by around 24%, indicating an overall improvement of health. We also have the evidence of the bleomycin-induced idiopathic pulmonary fibrosis model; D+Q reduced fibrosis by 40% (Xu *et al.*, 2018). Fisetin (60 mg/kg) clears 40 to 65% of senescent cells and extended median survival by 28% in progeroid mice (Yousefzadeh *et al.*, 2018). Navitoclax, when given at 25 to 50 mg/kg, will effectively eliminate BCL-2-dependent senescent cells and improve bone parameters by approximately 25% in an osteoporosis model, so these findings show us that senolytics have a positive effect on various diseases (Sharma *et al.*, 2020).

Clinical Trial Evidence

IPF (NCT02874989): In 14 patients treated with D+Q (100 mg dasatinib + 1000 mg quercetin, 3 days/week for 3 weeks), walking distance improved by 17 meters, and blood markers of senescence (p16^INK4a) decreased by ~20%, with acceptable safety.

Diabetic Kidney Disease (NCT04042168): In 9 patients with type 2 diabetes and CKD, adipose tissue senescence markers (SA-β-gal) decreased by ~35%, while kidney function (eGFR) remained stable.

Alzheimer's Disease (SToMP-AD, NCT04685590): D+Q reduced cerebrospinal fluid markers of cellular senescence.

Frailty (NCT04313634): D+Q improved SPPB score by+0.4 pts.

Table 2 : Senolytic Pharmacokinetic Properties Table.

Senolytic	MW (Da)	LogP	Key Targets	PK Notes	Reference
Dasatinib	488.0	2.5	Src/FAK/ABL	C_{max} 100 nM, $t_{1/2}$ 4 hr	(Lorenzo *et al.*, 2023)
Quercetin	302.2	1.8	BCL-2, HSP90	C_{max} 1 ug/mL, $t_{1/2}$ 12 hr	(Wissler Gerdes *et al.*, 2021)
Fiestin	286.2	1.1	BCL-XL, PI3K	Bioavail 5%, $t_{1/2}$ 6 hr	(Lelarge *et al.*, 2024)
Navitoclax	823.4	6.2	BCL-2/ XL/W	C_{max} 2 uM, $t_{1/2}$ 15 hr, platelets decrease	(Zhu *et al.*, 2017)

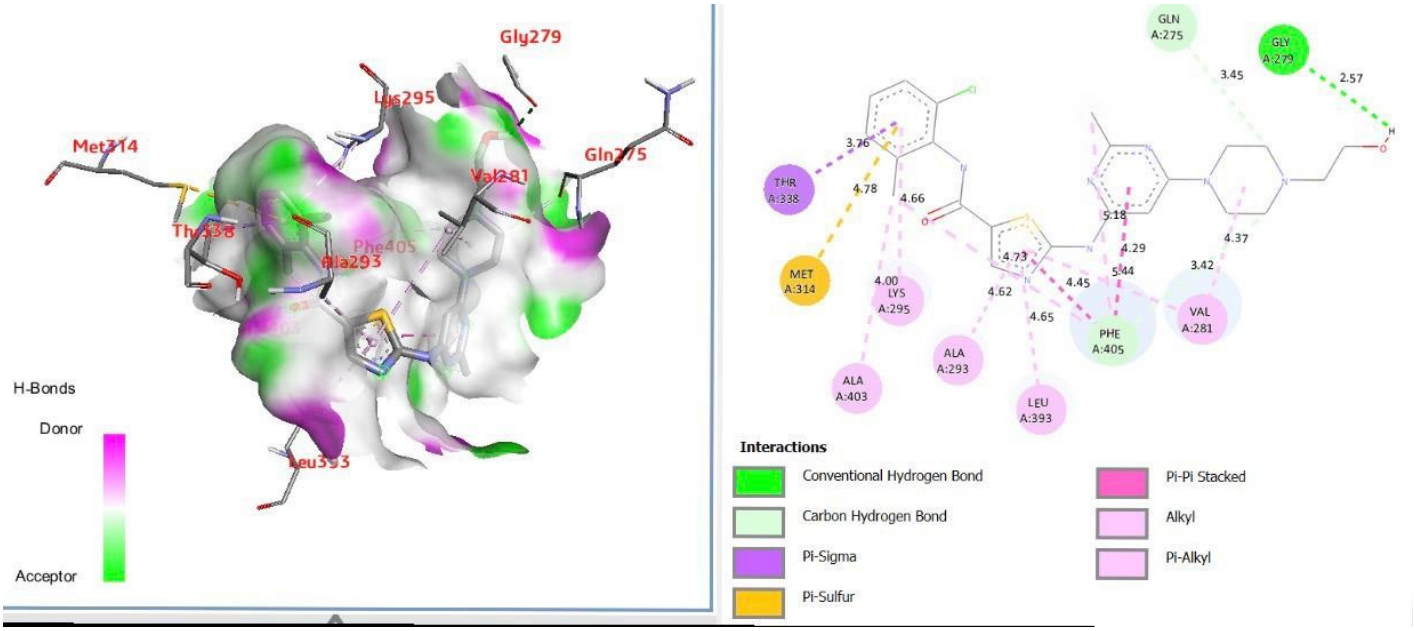


Figure 5: Navitoclax docking in BCL-2 active site showing apoptosis induction interactions.3D pose with H-bonds (green) and hydrophobic contacts (yellow); (B) 2D ligand interaction map (purple: π-stacking).

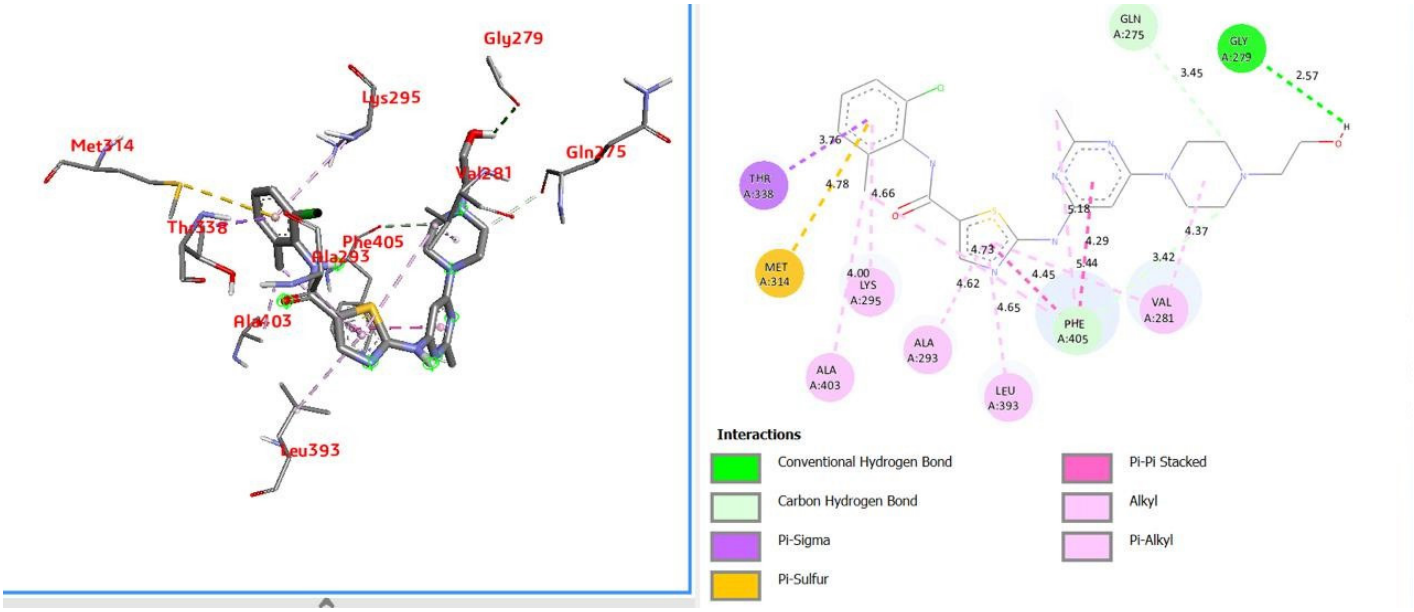


Figure 6: Navitoclax docking in BCL-XL site showing apoptosis interactions (A) 3D pose with H-bonds (green) and hydrophobic contacts (yellow); (B) 2D ligand interaction map (purple: π-stacking). Senescent cells drive various diseases including cancer, osteoarthritis, and diabetic nephropathy through SASP-mediated dysfunction.

CONCLUSION

Pharmacological targeting of cellular senescence through senolytic agents shows a very transformative potential in the treatment of various chronic disease pathophysiologies, from diabetes mellitus to neurodegenerative diseases to atherosclerosis. This review offers molecular mechanisms for the DDR/p53-p21 and p16-Rb pathways during SASP amplification with chemistry-driven strategies including quercetin, dasatinib, fisetin, and navitoclax. Structural activity relationship and docking studies also reveal interaction that enables apoptosis of senescent cells while sparing the healthy tissues.

Preclinical models also demonstrate a 50 to 70% clearance rate across. more than 10 diseases. Early clinical trials also confirm the safety of D+Q dosing, with the reduction of the biomarkers and functional gains. There are various problems that are associated with senescence. Navitoclax causes thrombocytopenia, fiestin bioavailability is poor, and there is SCAP resistance. There are also recent solutions being developed, such as biofunctional hybrids, where one drug hits the two targets when drugs like D + Q are given in combination. Drugs are being developed that basically activate the senescent cells that have high β-galactosidase enzyme, and nanoparticle formulations are being developed for better drug delivery into cells.

Future direction basically prioritizes the AI to design the improved senolytic drug structure; it also focuses on the development of a multitarget drug that attacks the several survival pathways and should also focus on conducting a large phase 3 clinical trial. These trials will check various senolytic cells in elderly patients who have multiple diseases rather than single diseases. This approach is very essential for a country like India, where we will have over 400 million people who cross the age of 60 by the year 2030.

ABBREVIATIONS

DDR: DNA Damage Response, a cellular signaling network activated by DNA lesions to maintain genomic integrity; **ROS:** Reactive Oxygen Species, chemically reactive oxygen-containing molecules that induce oxidative stress and DNA damage; **SASP:** Senescence-Associated Secretory Phenotype, a pro-inflammatory secretome released by senescent cells; **IL-6:** Interleukin-6, a cytokine involved in inflammation and immune regulation; **IL-8:** Interleukin-8, a chemokine that recruits neutrophils during inflammatory responses; **BCL-2:** B-cell Lymphoma 2, an anti-apoptotic protein family regulating cell survival; **PI3K/AKT:** Phosphoinositide 3-Kinase/Protein Kinase B pathway, a major intracellular signaling pathway controlling growth and survival; **SAR:** Structure–Activity Relationship, the relationship between chemical structure and biological activity of compounds; **HSP90**: Heat Shock Protein 90, a molecular chaperone involved in protein folding and stabilization; **NF-κB:** Nuclear Factor Kappa B, a transcription factor regulating inflammation and immune responses; **ATM:** Ataxia Telangiectasia Mutated kinase, a DNA damage sensor activated primarily by double-strand breaks; **ATR:** ATM and Rad3-Related kinase, a DNA damage sensor activated mainly during replication stress; **CHK1:** Checkpoint Kinase 1, a kinase involved in cell cycle arrest following DNA damage; **CHK2:** Checkpoint Kinase 2, a kinase mediating DNA damage checkpoint signaling; **p21^CIP1:** Cyclin-Dependent Kinase Inhibitor 1, a cell cycle inhibitory protein induced by p53; **CDK4/6:** Cyclin-Dependent Kinases 4 and 6, enzymes regulating G1/S phase cell cycle progression; **RB:** Retinoblastoma protein, a tumor suppressor controlling cell cycle progression; **E2F:** E2F Transcription Factor family, regulators of genes required for DNA synthesis; **SAHF:** Senescence-Associated Heterochromatin Foci, condensed chromatin structures associated with stable senescence.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Sharma S, Chettri B, Shree RK, Namana G, Rakshitha NP, Thomas BB, *et al*. Pharmacological Targeting of Cellular Senescence: Molecular Mechanism and Anti-Ageing Strategies in Chronic Diseases Pathophysiology. J Young Pharm. 2026;18(2):300-9.