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Senolytics: Therapeutic Strategies for selective Elimination of Scenescent Cells

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ABSTRACT

AIM& Objective: This report will summarize the present situation of the art of senolytics as innovative therapies for selective destruction of normal senescent cells in order to attenuate aging and age-associated maladies, identifies the inducers of cellular senescence and distinguish the distinct phenotypes of senescence cellular types, highlight important senile cell anti-apoptotic pathways (SCAPs) that can be utilized primarily for drug development, and discuss different families of senolytic drugs, their mechanisms for action, alongside the current status of how they are being developed for clinical applications.

Methodology: Articles with peer reviews from PubMed, Scopus and clinical trial databases pertaining to cells senescence, SCAPs and senolytic therapeutics was analyzed to generate the present review. Records on senescence triggering conditions such as DNA degradation, conventional oxidative stress, tumor-promoting activation and persistent inflammatory responses were analyzed. We assessed hallmark senescent phenotypes such as cell cycle arrest mediated by p16,INK4a and p21,CIP1, SA-β-galactosidase activity, and the Senescence-Associated Secretory Phenotype (SASP). Major families of senolytic drugs were classified based on their molecular targets, including BCL-2 inhibitors (e.g., navitoclax), tyrosine kinase inhibitors (e.g., dasatinib), flavonoids (e.g., fisetin and quercetin), HSP90 inhibitors, FOXO4-p53 modulators, and galactose-conjugated prodrugs. Effectiveness and security were measured using preclinical as well as preliminary clinical trial data.

Conclusion: Senescent cell building up causes tissue degeneration due to SASP-mediated inflammation and fibrosis. Senolytics capitalize of the truth that senescent cells normally rely on SCAPs to maintain their survival, and consequently, they can deliberately kill senescent cells as opposed to cells that are normal. The original agents such as dasatinib + quercetin have curative properties in models of idiopathic pulmonary fibrosis, osteoarthritis and neurodegeneration. Second-generation senolytics are developed to increase cell-type differentiation and lessen toxicity. The intention of SCAPs is a promising medicinal approach to delay age-related diseases and increase healthspan; however, therapeutic translation is hindered by the absence of biomarkers, dosing issues and the concern of long-term health risks.

Keywords: Senolytics; Cellular senescence; SASP; SCAPs; Drug targets; Aging

ABBREVIATIONS

I. Introduction

Aging is a natural process of the body that is characterized by a progressive decline in physiological integrity that leads to loss of function and vulnerability to death. Among the various cellularand molecular mechanismsthat contributetoaging, cellularsenescence hasemergedasa fundamental driver of age-related dysfunction and chronic disease[1], [2]. The evidence is growing that most of the chronic diseases and geriatric syndromes have pathways that overlap with ageing and that these pathways can be modified.ThisGeroscience Hypothesisarosefrom theobservationthatagingisthegreatestriskfactorformostchronicdiseases,suchas cardiovascular disease, type II diabetes, cancer, and many degenerative and neurodegenerative disorders [3]. Older age is the single most important risk factor for most of the chronic diseases responsible for most morbidity, mortality and health expenditures in the world [4], [5]. The main advantage of looking at aging throughthe lens ofthe Geroscience Hypothesis is that, iftrue, then by targeting these sharedaging

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mechanisms, itmaybe possible toprevent, delay andperhaps even reverse multipleaging-relatedconditionsandphenotypes simultaneously[6]–[8].Suchinterventionswould increasethehumanhealthspan (quality,healthy,independent, productive yearsoflife),while decreasingtheburdenoflongdisease-riddenyearslaterinlifeonbothcaretakersand economy[9], [10]. These chronic diseases include atherosclerosis and other cardiovascular diseases, strokes, dementias, most cancers, diabetes, renal failure, chronic lung diseases, osteoporosis, arthritis, blindness and neurological disorders. In addition, an older person's risk of developing geriatric syndromes and loss of physical resilience increases with age. Geriatric syndromes include frailty, sarcopenia, immobility, falls, depression, moderate cognitive impairment, incontinence, metabolic syndrome and weight loss. Factors that may indicate a lack of physical resilience include delays in recovery following myocardial infarction, stroke injuries, infections, chemotherapy, surgery, fractures, and poor vaccination response. Combinations of these conditions often occur in older individuals, with the frequencyof multimorbidity (three or conditions occurring simultaneously) increasing exponentially inthe third tertile oflife[11]. The potential benefits of treating any one age-related condition are complicated by the existence of multimorbidity[12]. Senescent cells secrete a varietyof bioactive molecules collectively known as the senescence-associatedsecretoryphenotype(SASP), whichincludespro-inflammatorycytokines, chemokines, growth factors, and matrix-remodeling enzymes[13], [14]. These factors have a dual nature:although theycan be beneficial inshort-term physiological contexts,such as promotingtissuerepairorhaltingtheproliferationofpre cancerouscells,theirlong term persistence fosters a deleterious milieu that disrupts tissue homeostasis, impairs stem cells function and promotes chronic inflammation and fibrosis.

The SASPisnow recognized asa key mediator of the “inflammaging” process, a low-grade, chronic inflammation associated with aging, and has been implicated in a broad spectrum of diseases, including osteoarthritis, atherosclerosis, neurodegeneration, diabetes, and cancer [15], [16].

Senescent cells, which exhibit irreversible growth halt and frequently secrete pro-inflammatory substances known as the senescence-associated secretory phenotype (SASP), are important causes of aging. Chronic senescent cell accumulation causes tissue malfunction, inflammation, and age-related decline, whereas transitory senescence helps with tissue repair and tumor suppression. Kondratyeva et al. (2025) demonstratedthat treatment with growth differentiation factor 11 (GDF11) partially reversed the senescent phenotype in mesenchy mal stem cells (MSCs), improving viability and angiogenic function[17]. The heterogeneity of senescent cellpopulations, the context-dependent effects of senescence, and the potential off- target consequences of eliminating or altering senescent cells raise concerns about the safety and specificity of current approaches [18]. Moreover, the lack of robust biomarkers to identify and monitor senescent cells in vivo complicates both research and clinical application[19]. As we continue to explore the complex biology of cellular senescence and refine our strategies for intervening inthisprocess,targeting senescence holdssignificant promise not onlyfor mitigating the effects of aging but also for transforming the way we approach the prevention and treatment of age-related diseases [20]

Cellular Senescence

Cellular senescence is a biological process observed in eukaryotic and some prokaryotic cells [21]–[23]. It describes the irreversible cell cycle arrest brought on by either endogenous or external stressors, such as telomere shortening and chronic or irreversible DNA damage. This process prevents the proliferation of faulty or damaged cells and inhibits their inheritance. Aging is a stress response, the early stages of which may be due to one or more of the factors such as telomere erosion, DNA damage, oxidative stress, oncogene activation, mitochondrial dysfunction, radiation, or drugs [24]. As one of the key driving factors among thehallmarksofaging,cellularsenescenceisadrivingfor cefororganandorganismaging[5]. The most compelling evidence for the role of cellular senescence in aging is that sustained genetic or pharmacological elimination of SnCs extends the lifespan of naturally senescent mice. Both excessive generation and insufficient elimination of SnCs may lead to pathological senescence [25].

Majorfactorsinducingsenescenceinclude:

Oxidative stress: The oxidative stress hypothesis of aging has received a lot of attention lately. Itis based on the hypothesis that during aging cells lose their functions due to ROS- induced damage. [26]

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Telomere shortening: Telomere shortening is the first molecular characteristic linked to senescence. The formation of G-quar double-stranded bodies at telomeres from G-rich strandsmay lead to replication stagnation and collapse . This is a consequence of end-DNA replication (i.e., the DNA replication mechanism is unable to complete the synthesis of the very top of the linear chromosome, and telomeres shorten with cell division). In both dividing and non-dividing cells, telomere shortening can also result from oxidative damage and other end-processing events. Telomere dysfunction caused by telomere shortening, telomere structural collapse, or displacement of the telomere protective protein complex elicits a DNA damage response that leads to loss of cell proliferation, senescence, or apoptosis.[27]–[29]

Metabolic stress: These metabolic alterations support the senescent state and lead to redox imbalance. They are regulated by nutrient and Suppression of PI3K/AKT pathway energy sensing pathways, particularly mTORand AMPK signaling networks[30]. Chronic activation of mTOR signaling enhances anabolic metabolism, increases oxidative stress, and promotesthe synthesis of SASP factorsthroughthe IL-1α–NF-κB axis[31]. In contrast, AMPK responds to energy stress by inhibiting mTOR activity and promoting autophagyand catabolic pathways, which help to mitigate oxidative burden and delay the onset ofsenescence. By influencing glycolysis, mitochondrial activity, and the production of antioxidant enzymes, the tumor suppressor protein p53 also plays a role in the metabolic control of senescence. Experimental evidence from model organisms indicates that interventions targeting these metabolic pathways, such as caloric restriction or pharmacological mTOR inhibition, can restore metabolic homeostasis, suppress SASP expression, and extend bothhealthspanand lifespan[32].

Chronic inflammation: Inflammatory factors in SASP are key links between SnCs and inflammation, mainly including pro inflammatory interleukin 6 (IL-6), IL-8, and monocyte chemoattractant protein 1, which are regulated in an IL-1 dependent manner, and enzymes involved in extracellular matrix remodeling .SASP has a major influence on aging and age-related illnesses and embodies the traits of SnCs. Factors secreted by SnCs can enhance the senescence phenotype in an autocrine manner, but they canalso affect neighboring cells in a paracrine manner. SnCstrigger their fibrotic effects mainly through the secretion of SASP and pro-fibrotic factors, which have been observed in the context of skin wounds or senescent fibroblast accumulation after myocardial infarction, which functionally limits tissue fibrosis[33], [34].

Mitochondrial dysfunction: Redox equilibrium and energy metabolism are crucially regulated by mitochondria. Dysfunction of the electron transport chain (ETC), especially at complexes I and III, leads to electron leakage and excessive ROS production . These ROS can damage mitochondrial and nuclear components, inducing senescence through p53 and p21 activation. Senescent cells triggered by mitochondrial impairment often shift from oxidative phosphorylation to glycolysis (Warburg-like metabolism), exhibit altered mitochondrial dynamics, and display persistent SASP expression [35]–[37].

DNA damage: Although many cellular stressors can induce senescence, total DNA damage and damage at repeat sequences at the ends of chromosomes known as telomeres are hallmarks of aging that occur in endothelial cells with advancing age and are robust inducers of senescence. Furthermore, the consequences of these aging hallmarks extend beyond senescence because they can impair transcription, DNA replication, and lead to mutations[38]–[40].

SENESCENCEASSOCIATEDSECRETORYPHENOTYPE(SASP)

Senescence Associated Secretory Phenotype (SASP) is associated with senescent cells where in those cells secrete high levels of inflammatory cytokines, immune modulators, growth factors, and proteases[41]–[43] . SASP may also consist of exosomes (vesicle) and microvesicle containing enzymes, microRNA, DNA fragments, chemokines, and other bioactive factors.Solubleurokinase plasminogen actiator surface receptor is a part of SASPand hasbeenusedtoidentifysenescentcells forsenolytictherpy[44].

Cytokines are signaling proteins that help control inflammation in your body. In SASP cytokines CCL2 (MCP1)recruit macrophagesto removecancer cells. Althoughtransient expressionof SASP can recruit immune system cells to eliminate cancer cells as well as senescent cells,chronic SASP promotes cancer. [45]Chemokines are a broad class of proteins produced by many immune cells as well as other bodily cells. NK and T cells are drawn to

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the TME (Total mesorectal excision) by pro-inflammatory chemokines. The recruitment of these immune cells promotes the removal of senescent cells, reducing the buildup of cells that would otherwise promote tumor formation.[46]Growth factors encourage skin progenitor cells to multiply and produce new cells. Senescent cells' synthesis of SASP components during this phase can promote tumor development in nearby cells. SASP factors, such as IL-6 and IL-8, can triggerepithelial-mesenchymal transition (EMT), increasing cancer cells invasive and metastatic potential.[47]

The family of zinc-dependent extracellular matrix (ECM) remodeling endopeptidases known as matrix metalloproteinases (MMPs) is capable of breaking down nearly all ECM constituents. SASP components can increase the production of matrix metalloproteinases (MMPs), which break down the extracellular matrix (ECM) and make it easier for SCC cells to invade nearby tissues.SASPfactorscanrecruitimmunecellssuchasmacrophagesand neutrophils which can paradoxically support tumor growth and invasion through therelease of growth-promoting and pro-angiogenic factors.[48], [49]

By causing paracrine senescence in nearby healthy cells, chronic low-grade inflammation in SASP can increase the number of senescent cells and strengthen a self-sustaining inflammatory network. As a result, ASAP is a central driver of chronic low-grade inflammation, referred to as inflammaging[41], [50], [51]Insulinresistance becausethe SASP includes macrophagesattractant proteinssuchasMCP1, it is possible that senescent cells in adipose tissue could be a driver of the macrophages infiltration that has been proposed to play an important role in adipose inflammation leading to insulin resistance in obesity.[52], [53]Adipose tissue dysfunction senescent cells also accumulate in the adipose tissue of mice and humans, and secrete multiple SASP factors that have been shown to induce cell death, increased local and systemic inflammation and recruitment of immune cells, leading to adiposedysfunction, insulin resistance and type-2 diabetes[54], [55].

WHATARESENOLYTICS?

A senolytics (from the word seno means “senescence” and lytic means “decomposition or breakdown”) is among a class of small molecules under basic research to determine natural compounds such as flavonoids and repurposed anti-cancer agents which are selective induce deathofsenescentcellsandimprovehealthinhumans.[56]Agoalofthisresearchistodiscover or develop agents to delay, prevent or reverse age related diseases.[57]. Removal of senescent cells with senolytics has been proposed as a method of enhancing immunity during aging.

Due to sedentary (lazy) lifestyles, an aging population, and complicated hereditary and environmental variables, metabolic illnesses such as obesity, Type-2 diabetes (T2D), and a metabolic syndrome are becoming more commonplace globally. A rising amount of research currently identifies cellular senescence as a key, age-related factor in metabolic dysfunction, a notion encompassing diseases of glucose and lipid metabolism.

The creation of seno-therapeutics, a group of treatments that comprise senolytics to eradicate senescence cells, seno-morphics to inhibit SASP, and seno-sensitizers to increase the susceptibility of resistant senescence cells to removal. A new age in medicine is about to begin. Because focusing on cellular senescence may significantly change how age-related metabolic problems are prevented and treated, perhaps improving longevity and lowering the burden of disease.

MECHANISMOF ACTIONOFSENOLYTICS

One component of aging and age-related illnesses is cellular senescence, a complicated cellular reaction to stress marked by a stage of cell cycle development. Numerous endogenous and exogenous factors, including as DNA damage brought on by oncogene activation, mitochondria and oxidative stress, pharmacological cytotoxicity, ionizing radiation, bacterial toxins, and viral infections, can cause cellular senescence. There is emerging evidence that accelerated aging and age-related diseases such as chronic autoimmune inflammation, hypertension, diabetes mellitus type-2, arthritis and cancer are negatively affected by the persistent presence ofsenescent cells.[58]Senolytics acts through several mechanism:

- **InhibitionofBCL-2familyproteins**

The primary regulators of the intrinsic apoptosis pathway are known to be members of the B-cell lymphoma 2 (BCL-2) family of proteins; proapoptotic proteins promote the induction of programmed cell death, while antiapoptotic proteins stop apoptosis from occurring. Consequently, the survival and resistance of cells to an apoptotic signal depend on the presence or lack of these proteins.

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However, BCL-2 family proteins also exert other non-canonical function affecting cellular senescence, bioenergetic metabolism and redox homeostasis.[59]Cellular senescence, often known as "senescence," is a protracted cell cycle-induced pause of formerly replicative cells. BCL-2 family members play a part in this process. Senescence might be a substitute for apoptosis in the suppression of cell proliferation. Senescence and apoptosis are both important in cancer. Senescence stops cancer cells from dividing permanently, but apoptosis destroys cancer cells.

BCL-2 familyproteinsare keyinthe resistance tochemotherapeutic, agents insome cancer cells, regulate cancer cell survival after prolonged mitotic arrest.[60] and are involved in the persistence of tetraploid cells by preventing the senescence program associated with tetraploidization.[61]. Therefore, using BCL-2 family inhibitors that belong to the class of "senolytics," or compounds with the ability to kill senescent cells, is one potential strategy .

SuppressionofPI3K/AKTpathway

PI3K (phosphatidylinositol kinase) is a dimer that composed of regulatory subunit p85 and catalytic subunit p110. PI3K can alter the structure of Akt and cause it to become phosphorylated (p-Akt) when it binds to growth factors, cytokines, or hormone receptors. p-Akt is the activated state of Akt that could regulate FoxO, mTOR and other signal proteins in its downstream.[62] PI3K/Akt is a classic pathway that plays an important regulatory role in cell proliferation, apoptosis, and autophagy. [63] Meanwhile, an increasing number of evidence show that the activation ofPI3K/Akt is also involved in stabilizing senescent cells.[64]shown in figure 2

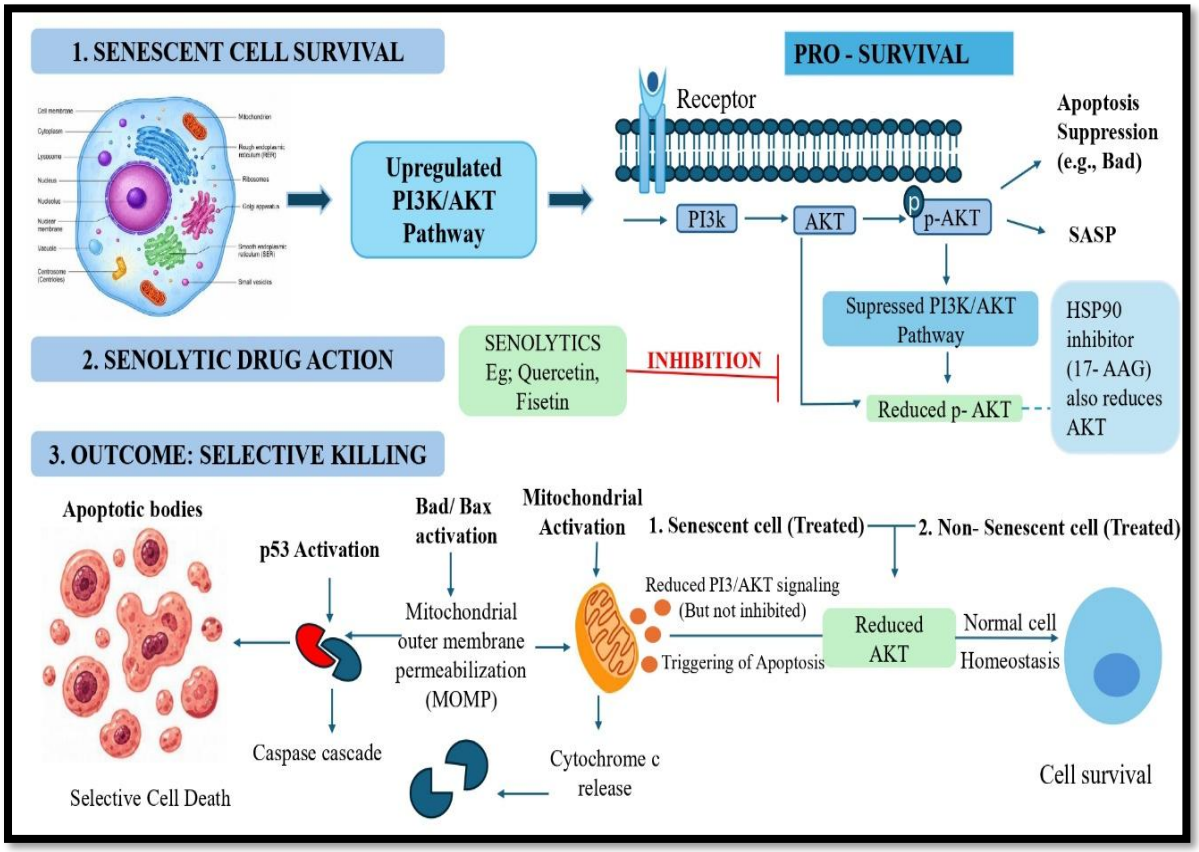

Figure:1Senolyticsactingthroughsuppression ofPI3K/AKTpathway

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Interferencewithp53pathways

As a protector of the genome, P53 suppresses tumors by controlling several downstream pathways related to cell cycle arrest, DNA repair, apoptosis, and cellular senescence. While cancer cells can be killed by p53-mediated apoptosis, it is becoming evident that cellular senescence plays a part in p53-dependent tumor suppression. Post-translational modification is the main mechanism that controls the amount and activity of p53 protein (fig. 2). The short-lived protein p53 is constantly being broken down by proteins and is susceptible to pro-teasomal degradation in a typical cell. Mouse double minute 2 (MDM2,HDM2 in human),one of the first characterized p53 targets, serves as a major E3 ubiquitin ligase for p53 degradation and thus forms a negative autoregulatory loop to maintain the low level of p53 expression in unstressed condition[65], [66].

In response to various stress signals, p53 plays a role in cellular senescence. It is controlled by phosphorylation (ATM/ATR-Chk 1), acetylation (p300/CBP, PCAF, Tip60/HMOF, a SIRT 1), enhanced protein stability (ARF-MDM2), and higher translation rates (RNCP1, Hur, and RPL26). When p53 is active, it controls a number of downstream targets that result in cellular senescence and other reactions related to cellular senescence. A number of indicators that are known to be p53 target genes that encourage cellular senescence include p21, PML, PAI-1, and DEC1.

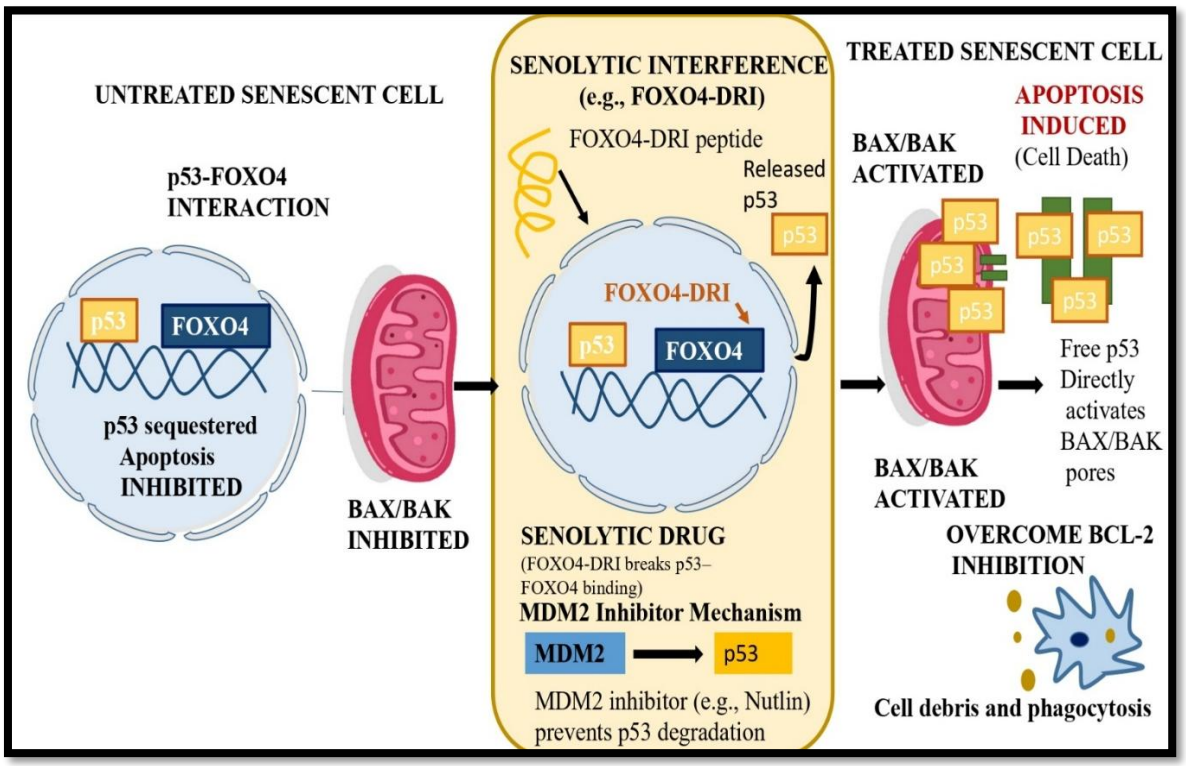

Figure:2 Senolyticsactingthroughinterferenceofp53pathway.

Targetingtyrosinekinasesignaling

By triggering anti-apoptotic signaling pathways, also known as senescent cell anti-apoptotic pathways (SCAPs), which set them apart from their healthy counterparts, senescent cells avoid immune clearance. Senolytic agents exploit this vulnerability by disabling these pro- survival mechanisms, thereby triggering apoptosis selectively in senescent cells while sparing non- senescent tissues[67],[68].

The first generation ofsenolytic therapies emerged with the identification ofdasatinib, a tyrosine kinase inhibitor and quercetin, a flavonoid that inhibits PI3K and other kinases[69]. (shown in table1) These two compounds, used in combination (D+Q), were found to clear senescent pre- adipocytes and endothelial cells in mouse models[70].Intermittent D+Q injection enhanced physical function,

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decreased the load of senescent cells, and occasionally increased longevity in old or sick animals.

Table:1A comparative analysis of the main groups of senolytics

Senolyticclass	Molecular target	Representtarget	Modeof action	Strength	Limitation/ challenges
Tyrosine kinase inhibitors	Src family kinase,Ephreceptors	Dasatinib	Inhibitspro-survival tyrosine kinases upregulated incertain SnCtypes	Effective in senescent preadipocytes and progenitors	Cell-typespecificity; potential for systemic toxicity.
Flavonoid polyphenols	PI3K/AKT, ROS pathways	Quercetin,Fisetin	Induces apoptosisvia oxidative stressand suppression of an ti-apoptotic signaling	Low toxicity,orally bioavailable, broad applicability	Variable potency: poorbioavailability invivo
BCL-2 family inhibitors	BCL-2, BCLxl, BCL-w	Navitoclax(ABT-263),ABT-737	Blocks an ti- apoptotic proteins, sensitizing SnCs to apoptosis	Potentand broad-acting across senescent phenotypes	Thrombocytopeniadue to BCL-xl inhibition in platelets
FOXO4- p53disruptors	FOXO4-p53complex	FOXO4-DRI peptide	Disrupts nuclear retention p53, restoring	SelectiveSnCclearance; rejuvenates aged tissues	Peptidedelivery limitations, currentlypreclinical
CDK/p53 pathway modulator	MDM2- p53, CDK4/6	UBX0101, Nutlin-3	Modulates cell cy cle regulators andapoptotic checkpoint	Targeted for local intra-articular applications	Short half-life, mixedclinicaltrial results
HSP90 inhibitors	Heat shock protein 90	17-DMAG, geldanamycin-n derivatives	Destabilize -s chaperone-dependant survival proteinsin SnCs	Targetmultiple stress response pathways	General cytotoxicity, lacks SnCspec ificity
CDK/p53	MDM2- p53, CDK4/6	UBX0101, Nutlin-3	Modulates cell	Targeted for local intra-	Short half-life, mixedclinicaltrial

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pathway modulator			cycle regulators andapoptotic checkpoint	articular applications	results
Natural senolytics(plant derived)	ROS generation, SASP factors	Piperlongumine, curcumin analogues	Promotes redox imbalance and down regulates SASP-related pathway	Low-cost, multitargeted, dietary sources	Low potency, unclear pharmacokinetics and dosing strategies

Modulationofmitochondrialpathways

Mitochondria, often referred to as cellular powerhouses, are crucial regulators of cellular energy production and intracellular signaling[71]. Numerous physiological processes, including DNA damage, cell-cycle arrest, the development of a senescence secretory phenotype, mitochondrial failure, autophagy/mitophagy dysfunction, signaling disorders, and intracellular communication, are linked to cellular senescence. However, a decline in mitochondrial activity is one of the primary pathophysiological causes of aging in cells and organisms.

Cell senescence may be both a cause and an effect of mitochondrial failure. Apoptosis may occur in cells that accumulate malfunctioning mitochondria because they are unable to meet energy needs. Furthermore, elevated ROS levels may trigger other stress pathways and alter senescence signals, exacerbating the aging process. As a result, mitochondrial malfunction and cell senescence are related, resulting in a vicious cycle where each condition worsens the other[56]. Reactive oxygen species generation rises, oxidative phosphorylation efficiency declines, and defective mitochondria develop in senescent cells. Adenosine triphosphate (ATP), a high-energy molecule that provides a universal source of energy for biochemical processes, is produced when foods are oxidized in mitochondria.

Electron leakage and an overabundance of reactive oxygen species might result from a malfunctioning electron transport chain. Increased ROS levels hasten the deterioration of important cell constituents, such as DNA, protein structure, and lipid membranes, which helps trigger cellular senescence processes and start the emergence of chronic inflammatory conditions. Apoptosis activation signaling pathways or "somatic senescence," a non-proliferative but metabolically active cell signaling mechanism linked to inflammation, are triggered by mitochondrial malfunction. They contribute to the development of inflammation by activating the mitochondrial pathways of inflammasome activation when they are damaged.

COMMONSENOLYTICAGENTS

A class of medications known as senolytics lessens the effects of cellular senescence, which is linked to a number of chronic and age-related illnesses. The number of recognized senolytic drugs has increased significantly since the first senolytics were discovered in 2015. The general categories of known senolytics—kinase inhibitors, Bcl-2 family protein inhibitors, naturally occurring polyphenols, heat shock protein inhibitors, BET family protein inhibitors, P53 stabilizers, repurposed anti-cancer, cardiac steroids, PPAR-alpha agonists, and antibiotics—are covered in this review. A variety of techniques to induce senescence, distinct target cell types, tests, and markers for senolytics are described as ways used to screen for novel senolytics.

A class of medications known as senolytics lessens the effects of cellular senescence, which is linked to a number of chronic and age-related illnesses. Current senolytics and screening methods for finding new active compounds are covered in this study. In the end, senolytic activity may vary on the kind of cell and the test, necessitating thorough validation. Ongoing investigation into therapeutic targets and assessment in preclinical and clinical trials are necessary for additional medication discovery.

Senescent cells are defined by a permanent cessation of cell division. These cells can exhibit features associated with G1 and G2 growth phases of the cell cycle, distinguishing them from both quiescent and terminally different cells[72]. Age-

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related dysfunction is closely associated with the buildup of senescent cells in mammalian tissues and organs. This is attributed to a senescence-associated secretory phenotype(SASP), which is characterized by the expression ofpro-inflammatory cytokines, chemokines, growth factors, matrix metalloproteinases, bioactive lipids, and other factors that promote tissue dysfunction and chronic low-levelinflammation[63]. Changes in mitochondria, lysosomaland endoplasmic reticulumactivity also occur[73]. Moreover, increased expression of negatively regulators of apoptosis and anti- apoptotic genes promotes the survival of senescent cells[74]. But the changes that take place during senescence are intricate, with a great deal of variation over time across cells and even inside the same cell.

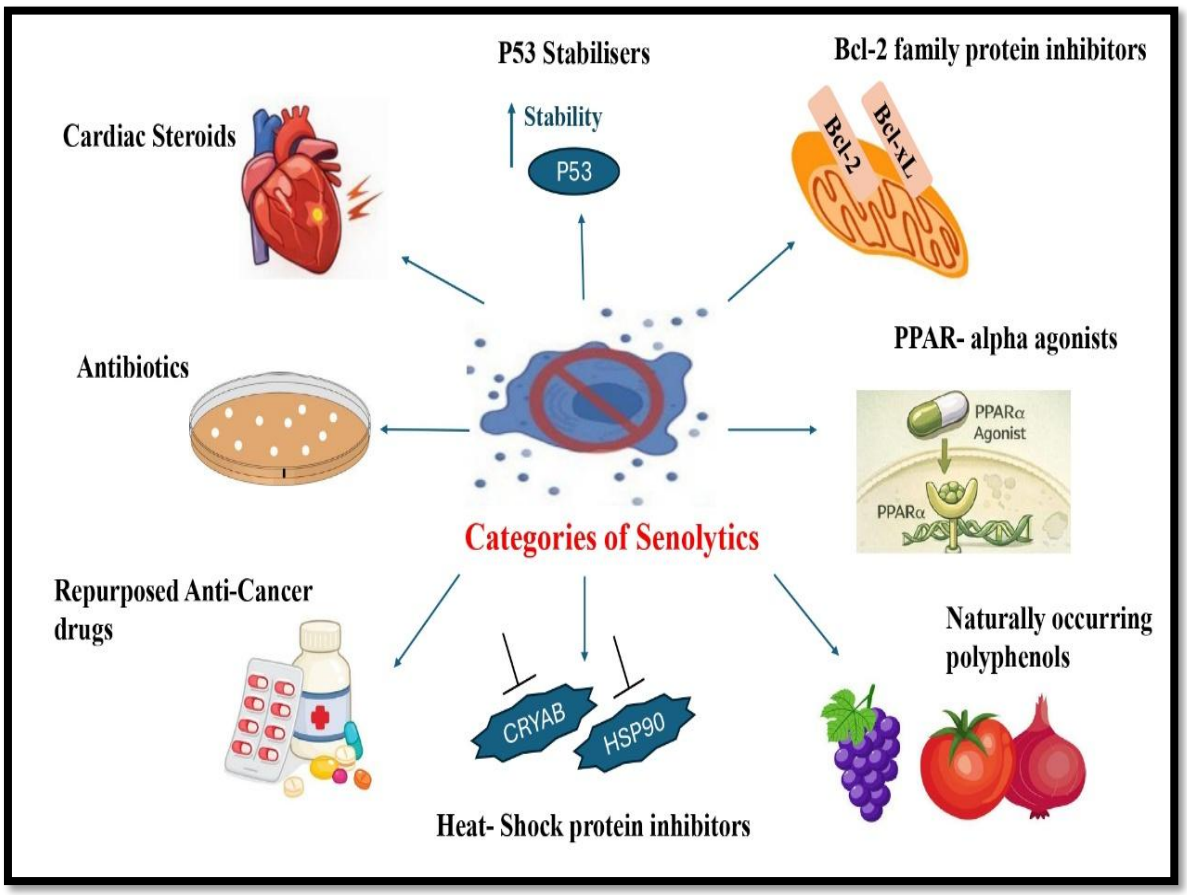

Figure:3 CategoriesofSenolytics

Repurposedanti-cancer drugs

Senescent and cancer cells have many characteristics in common, despite the fact that cellular senescence and the unchecked growth seen in cancer are very different. These include altered metabolism, resistance to apoptosis and increased autophagy.[75]

- **Cardiacsteroids**

The senolytic activity of cardiac steroids was identified by two separate studies that usedhigh-throughput screening to detect active compounds from commercial drud libraries[76].While a collection of natural products includes molecules with evolved interactions in a biological system and can have a high molecular diversity, pharmacologically active drug libraries comprise compounds with a variety of bioactivities and recognized pharmacokinetic features.

- **PPAR-aagonists**

The novel bioactivity of fenofibrate (a peroxisome proliferator-activated receptor α agonist) was uncovered via a unique screening approach focused on therapeutics for cartilage degenerationand osteoarthritis[77].

- **Antibiotics**

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In human cells, the medicines azithromycin and roxithromycin have demonstrated some senolytic action. Thiswasrevealed ina screenof15 approved antibiotics ina modelfeaturing BrdU- treated MRC-5 and BJ fibroblasts[63].
Here is a breakdown of beneficial knowledge regarding the specific drugs and natural compounds:

Naturalcompounds(Flavonoids)

These compounds offer a "senomorphic" (SASP-suppressing) and senolytic approach, generally with fewer side effects.

- **Fisetin:** Fisetin, which is present in fruits like strawberries, is now regarded as one of the most powerful natural senolytics. Research indicates that it enhances insulin sensitivity, lessens the load of senescent cells in visceral adipose tissue, and lessens diabetic nephropathy (kidney disease).
- **Quercetin:** Present in onions and apples, it works by targeting anti-apoptotic proteins that senescent cells rely on for survival. It works best in combination with other agents (like Dasatinib) to disrupt survival pathways.
- **Curcumin:** Curcumin, which comes from turmeric, blocks the NF-kB pathway, which is a crucial SASP regulator(pro-inflammatory) production. It is particularly effective at reducing inflammation, a major driver of metabolic dysfunction.

Syntheticdrugs

- **Dasatinib (D):**A tyrosine kinase inhibitor that destroys endothelial cells and senescent adipocytes (fat cells) and is authorized for leukemia.
- **Navitoclax (ABT-263):** A BCL-2 family inhibitor that causes senescent cells to undergo apoptosis. Navitoclax dramatically increased beta-cell activity and insulin sensitivity in mice, according to preclinical studies.
- **FOX04-DRI Peptide:**A specially created peptide that releases p53 to start apoptosis solely in senescent cells by precisely disrupting the connection between FOXO4 and p53. In elderly mice, it has been demonstrated to enhance kidney function and restore tissue homeostasis.
- **Combination therapy:**Quercetin + Dasatinib (D+Q) Currently undergoing early-stage human clinical studies, this is the most extensively researched senolytic combination (e.g., for diabetic kidney disease).

ROLEOFSENOLYTICS INMETABOLICDISORDER

Senolytics are a potential class of therapeutic medicines that reduce the detrimental effects of senescent cells on surrounding tissues by specifically inducing their death. A family of medications known as senolytics reduces chronic, low-grade inflammation (SASP) and reverses metabolic inefficiency in diabetics and obese people by specifically eliminating senescent cells.
Hereisadetailedbreakdownofhowsenolyticsimprovingmetabolic health:

- **Reducinginsulinresistance**

Cellular senescence is thought to play a role development of insulin resistance and diabetic complication however, the diabetics state can also cause formation of additional senescent cells, for example- through exposure to high glucose or lipid levels, which can themselves cause cellular senescence [78]. Senescent cells possess the ability to evade apoptosis through upregulationofanti-apoptoticpathways, includingthe PI3K/AKT, P53/P21 CIP1/serpin, HIF- 1a and BCL-2/BCL-XL pathways [79].

- **Improvingglucosemetabolism**

Disturbance in glucose metabolism can also induce cellular senescence and SRSPs in various tissues, such as pancreatic beta cells, endothelial cells, neurons, astrocytes, myocytes and adipocytes[41].Thesefactorscanregulatevariousaspectsofglucosemetabolismsuchas

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glycolysis, gluconeogenesis, glycogensynthesisandbreakdown,pentosephosphatepathway,and the hexosamine biosynthetic pathway. SRSPs can also impair glucose uptake and utilization in these tissues by interfering with insulin signaling and inducing insulin resistance.[41]

- **Decreasinginflammation**

The immune system is not the only source of pro and anti-inflammatory substances, even though it plays a significant role in regulating their levels. Cellular senescence is associated with a substantial increase in the production of 40–80 factors involved in intercellular communication, according to recent studies in fibroblasts and epithelial cells.[58] SASP proteins, which include a variety of growth factors, proteases, chemokines, and cytokines, are often activated at the m-RNA level. Proteins that are known to stimulate inflammation, includingIL-6,IL-8, IL-1, granulocyte macrophage colony-stimulating factor (GM-CSF), growth regulated oncogene (GRO)a, monocyte chemotactic protein MCP-2, MCP-3, MMP-1, MMP-3 and many insulin-like growth (IGF) binding proteins are among the most sharply induced and secreted of these factors.[80]

- **Restoringadiposetissuefunction**

Adipose tissue's delicate function at the organ and systemic levels is crucial in controlling glucose homeostasis and whole-body energy. On the one hand, adipose tissue regulates the body's distribution and metabolization of fats and stores energy in the form of fats. Conversely, adipose tissue functions as an endocrine organ and generates a variety of bioactive substances, including adipokines, which interact with other organs and alter various metabolic pathways.

It is becoming more widely acknowledged that adipose tissue, which is mostly made up of adipocytes as well as pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leucocytes, plays a significant role in systemic metabolic control. As the fuelreservoir, adipose tissue conserves the heat of the body and controls the lipid mobilization.[81]

- **Enhancingmitochondriaactivity**

The importance of mitochondria in the aging process is becoming more well recognized. A major factor in biological aging is mitochondrial dysfunction, which is defined by a decreased oxidative capability and an increase in oxidative damage[82]. The only known cell organelles with DNA that is different from nuclear DNA are mitochondria (also known as mitochondrial DNA, or mt-DNA, n-DNA).

SENOLYTICSINSPECIFIC METABOLIC DISEASESOBESITY

Cardiovascular and metabolic disorders are significantly exacerbated by obesity. The significance of senescence in obesity-induced metabolic diseases and cardiac dysfunction is still unclear, despite the fact that senescent cells have been demonstrated to accumulate in adipose tissues. Consequently, the therapeutic potential of regulating senescence in obesity-related metabolic and cardiac illnesses remains unclear.

The accumulation of body fat associated with this condition impairs health and reduces life expectancy; it is also associated with an increased risk for severaldiseases [83] includingtype

2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease and other cardiovascular disorders. Although obesity may be influenced by other factors [84] it is mainly caused by an imbalance between caloric intake and energy expenditure due to the high consumption of a hypercaloric diet associated with reduced physical activity.

During obesity, chronic and excessive consumption of saturated fatty acids, cholesterol, added sugars etc generates a chronic inflammatory response in multiple organs, including the brain [85]. Systemic inflammation induces neuroinflammation and alteration in brain structures, such as the cerebral cortex(cx) and hippocampus (Hc) mainly related to learning and memory process[86]. Senolytics combat obesity by selectively eliminating senescent cells that accumulate in adipose, tissues, reducing chronic, low-grade inflammation. These agents improve metabolic function by lowering insulin resistance, reducing fat mass expansion and mitigating obesity-related cardiac dysfunction, primarily through reducing inflammation and improving adipose tissue health.

- **Senescentcellsaccumulateinadiposetissue**

Adipose tissues Diabetes and insulin resistance linked to obesity are linked to inflammation and dysfunction. Removal of senescent cells from obese animals either through genetic means targeting p21cip1 or p16ink4a expressing cells or with senolytic drugs, improves whole body and adipose insulin sensitivity, indicating that senescent cells likely contribute to obesity- related metabolic dysfunction [87]. In addition, several measures od adipose tissue function improve with senescent cells

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removal, including decreases in adipocyte size, improvedadipogenic potential and decreased macrophage infiltration .

Adipose tissue, the main location for lipid storage, has drawn more attention as an endocrine and metabolically active organ due to obesity and associated metabolic disorders. The tissue with the greatest potential to store extra energy is subcutaneous adipose tissue; when this capacity is achieved, hypertrophic obesity, local inflammation, insulin resistance, and

Type 2 diabetes will eventually appear. Due to the incapacity to attract and differentiate new mature adipose cells, hypertrophic adipose tissue is also linked to dysfunctional adipogenesis. Dysfunctional cells, elevated inflammation, reduced insulin sensitivity, and fat accumulation are characteristics of senescent adipose tissue.

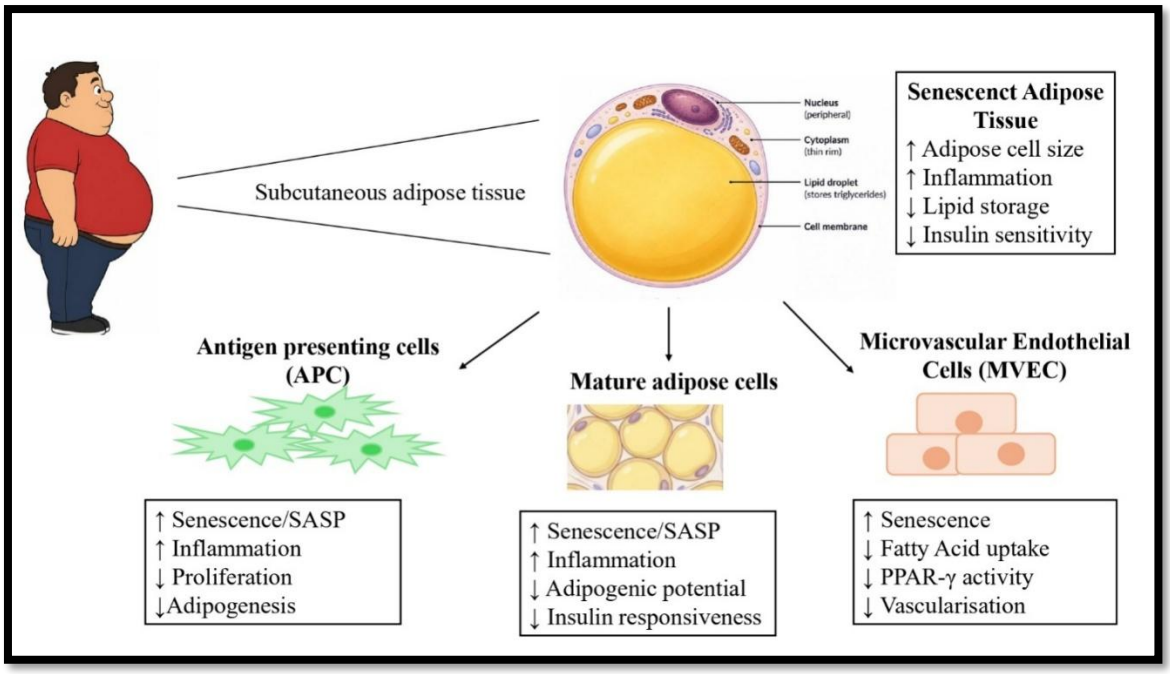

Figure4: Impactofcellularsenescentinadiposetissue

Senolyticsreducesinflammationandimprovefatmetabolism

Senolytics are medications that specifically eliminate senescent cells, which are dangerous cells that prevent self-destruction and defend themselves against their inflammatory secretion, sometimes referred to as the senescence-associated secretory phenotype (SASP). Senolytics, which selectively target senescent cells with an SASP, cause these cells to self-destruct by obstructing their defense systems.

By taking advantage of the cells' susceptibilities to certain stresses, senolytics eradicate senescent cells. Senescent cells frequently have a greater baseline level of stress because of things like DNA damage, mitochondrial malfunction, and the pro-inflammatory state linked to the SASP, even if they are resistant to apoptosis through anti-apoptotic pathways. Certainsenolytics target and amplify these stressorsorinhibittheprotectivepathwaysthatsenescentcellsrelyontosurviveundersuch stress. This is used in mitigating arthritis, such as fisetin and quercetin, target and remove senescent cells linked to joint inflammation and degeneration.

Type2diabetes

The pathogenesis of type 2 diabetes is mostly influenced by increased insulin resistance and decreased insulin production. Peripheral tissues including muscle, liver, and fat exhibit insulin resistance signaling. Insulin resistance is accelerated byobesityaccompanied byaccumulation of dysfunction adiposetissues,followedbycompensatoryincreaseininsulinsecretion.

Subsequently, declines in pancreatic beta-cell function develops diabetes mellitus in susceptible

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subjects [88]. Amounts and functions of adipose tissues are affected by aging as well as by calorie intake, physical activity and aspects of health status[89]. It is also known that insulin secretion decreases with aging.

Chronic hyperglycemia brought on by insulin resistance and insufficient insulin production is the hallmark of type 2 diabetes, a metabolic disease. T2D is the most prevalent kind of diabetes, making for 90–95% of all cases diagnosis. Without prompt management, T2D can lead to severe complication including cardiovascular diseases, nephropathy, neuropathy and retinopathy. Standard treatments typically involvelifestyle intervention, i.e., diet, exercise modifications, pharmacotherapy with agents such as metformin and insulin therapy to regulate blood glucose levels[90].

- **Improveinsulinsensitivityandpancreaticbetacellfunction**

Increased insulin resistance and impaired insulin secretion have central roles in the pathophysiology of T2D[91]. Impaired responses to insulin signaling in peripheral tissues such muscle, liver, and fat lead to insulin resistance. Obesity and the buildup of dysfunctional adipose tissues promote insulin resistance, which is then compensated for by an increase in insulin production. In susceptible individuals, decreases in pancreatic beta cell activity lead to the development of diabetes mellitus. Amounts and function of adipose tissue are affected by aging as well as by calorie intake, physical activity and other aspects of health status [88].Aging is known to be linked to increasing insulin resistance and cellular senescence in adipose tissue, both of which have an impact on the development and course of illnesses. Additionally, it is known that as people age, their insulin secretion declines. Systemic evaluation of insulin secretionis affected not only by the ability of individual beta cell to secreteinsulin,but also by the beta- cell mass[92]. Age-dependent decline in insulin secretion has been reported in studies using isolated human islets. BCM can be changed dramatically during the onset and progression of obesit1ayanddiabetesanddeclineofBCMcanheavilyinfluencethestatusofdiabetes,suchasglycaemiccontrolandresponsestoanti-diabetestreatment[93].

- **Non-AlcoholicFattyLiverDisease(NAFLD)**

One of the most prevalent liver illnesses, nonalcoholic fatty liver disease (NAFLD) affects around 25% of people globally. Its prevalence rises with age, obesity, and diabetes. Clinical and histological criteria, such as lipid buildup in hepatocytes—defined as steatosis in people who do cnot drink excessively—are used to make the diagnosiss. NAFLD frequently progresses to NASH which is characterized by the presence of steatosis, inflammation, necrosis and fibrosis[94]. Advanced fibrosis observed in some NASHpatients may lead to cirrhosis in 10-15% of these patients or even to hepatocellular carcinoma (HCC) [95].

- **Liverinflammationandfibrosis**

Obesity, metabolic syndrome and aging are major risk factors for a broad spectrum of chronic liver diseases, which typically follow a progressive trajectory fromsteatosis and inflammation to fibrosis, cirrhosis and ultimatelyliver failure orcancer[96].Hepatotoxins, genetic mutations, lip toxicity, and persistent viral infections like hepatitis B and C are just a few of the assaults that can cause the complicated, multifactorial process of cellular senescence in the liver. SASPs, which are defined by the prolonged release of pro-inflammatory cytokines, chemokines, growth factors, proteases, and extracellular matrix-modifying enzymes, are also adopted by senescent liver cells.

- **Metabolicsyndrome**

Central obesity, hyperglycemia (defined as insulin resistance or decreased glucose tolerance), hypertriglyceridemia, low HDL, cholesterol, and hypertension are among the metabolically risk factors that make up the Mets group of disorders. It is widely considered as a major risk factor for diseases such as diabetes, cardiovascular andcerebrovascular diseases [97]. One of the most important factors in the development of Mets is insulin resistance. Insulin–insulin receptor (IR) binding is significantly influenced by the insulin receptor substrate (IRS) protein. Insulin signaling components in the plasma membrane and internal membrane cisterna are activated when insulin stimulation causes active insulin receptor kinases to phosphorylate the IR and IRS. Typical insulin-induced metabolic effects, including enhanced glucose absorption, are produced by these signaling molecules, which also relay insulin signals. However, during cellular senescence, the level of intracellular oxidative stress is heightened, activating phosphorylation cascades, such as mitogen-activated protein kinase [98].

Preclinicalandclinicalstudies

Over the past few years, researchers have shown great interest in studying senolytic drugs and their

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potential role in improving health during aging. Preclinical studies, which are mainly show in animal models, have provided strong evidence that senolytics can remove senescent cells and improve overall body function. Senescent cells are aged or damaged cells that stop dividing but remain active in the body. These cells release harmful inflammatory substances that can damage surrounding tissues and contribute to many chronic diseases[77]

Table-1pre-clinicaltrialsofsenolytics[4], [99]

Senolytic Agent/ combination	**Experimental Model**	**Target/ Mechanism**	**Pre-clinicalresults**
Dasatinib+Quercetin	Aged mice, Adipose tissue cell	Inhibits anti-apoptotic pathways in senescent cells	Reduced senescent cell burden improvesphysical function and metabolic activity
Navitoclax(ABT-263)	Mouse hematopoietic stem cells	InhibitsBCL-2family proteins	Eliminated senescentstem cells andimprovedtissue regeneration
Fisetin	Agedmice	Antioxidant and apoptosis including activity	Reducedinflammation and extendedlifespanin animalmodels
Piperlongumine	Human fibroblast cellsand mice	Increases oxidative stressinsenescentcells	Selectively killed senescent cells whilesparing normalcells

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FOXO4-DRIpeptide	Progeroid and naturally agedmice	Disrupts FOXO4-P53 interaction	Cleared senescent cells and improved physical health and organ function
UBX0101	Mouse osteoarthritis model	Induces apoptosis of senescent chondrocytes	Reduced joint inflammationand improved cartilage condition

Age-related decreases in physical function indicate impending impairment, higher health care costs, and death. These effects of aging may be exacerbated by cellular senescence, which causes tissue malfunction. However, it is yet unknown if senescence may directly cause age-related disease and be therapeutically treated. Here, we show that introducing very few senescent cells into young mice is enough to disseminate cellular senescence to host organs and induce long-lasting physical impairments. Transplanting even fewer senescent cells had the same effect in older recipients and was accompanied by reduced survival, indicating the potency of senescent cells in shortening health- and lifespan.[63] In human adipose tissue explants, the amount of naturally existing senescent cells and their release of proinflammatory cytokines linked to frailty were reduced by the senolytic cocktail, dasatinib with quercetin, which selectively eliminates senescent cells. Additionally, intermittent oral administration of senolytics reduced mortality risk to 65% and improved post-treatment survival by 36% in both naturally aged mice and young mice transplanted with senescent cells. Our study provides proof-of-concept evidence that senescent cells cancause physicaldysfunction and decreased survivaleven in young mice, while senolytics can enhance remaining health- and lifespan in old mice[100].

In several animal studies, treatment with senolytic drugs has resulted in improved metabolic function, reduced inflammation, and even increased lifespan. By clearing senescent cells from tissues, these drugs help restore normal cellular activity and improve the functioning of organs such as the liver, muscles, and adipose tissue.

Oneofthemostwidelystudiedsenolyticcombinationsis DasatinibandQuercetin.This combination has been shown to effectively eliminate senescent cells in different tissues. Early humanstudiesusingthisdrugcombinationhaveindicate promisingresults,including improvementinphysicalperformanceandreduseininfl ammatorymarkers[10].

Table-2: Ongoingandplannedclinicaltrialsusingsenolyticdruginterventions

Intervention Treatment	Diseasecondition Outcomemeasures	Outcome measures	Eligible age	Phase
DasatinibQuercetin	Idiopathic pulmonaryfibrosis	Improvement in physicalfunction	≥50	Phase1
DasatinibQuercetin	Diabetes and kidney dysfunction	Decrease in senescence markers	50-80	Phase1
DasatinibQuercetin	Alzheimer's disease	Changeincellular senescence bloodmarker	≥65	Phase2
DasatinibQuercetin	Chronic kidney disease	Senescent cells proportional change	40-80	Phase2
Fisetin	Frailty, inflammation	Decreaseinblood inflammation markers	≥70	Phase2
Dasatinib Quercetinfisetin	Childhoodcancer and frailty	Senescence reduction and frailty improvement	≥18	Phase2
UBX0101	Osteoarthritis	Safety and efficacylevel	40-85	Phase2
UBX1967/	Macular	----	----	Planned

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UBX2050	degeneration			

Although these early clinical findings are promising, research in humans is still limited. Many clinicaltrials are currentlyunderway to evaluate the safety, effectiveness, and appropriate dosing of senolyticdrugs.Scientists are also investigating their potential use in treating metabolic diseases such as obesity, insulin resistance, and type 2 diabetes. After numerous preclinical studies highlighting the effectiveness of senolytics, several clinical trials are now underway. These trials aimto evaluatethe safety and efficacy ofsenolytic agents in humans, providing vital insights that could shape future anti-aging therapies and strategies.

Advantagesofsenolytics

Senolytic drugs have several important advantages in treatment and prevention of age-related diseases. Several factors can accelerate the accumulation of senescent cells, leading to cellular senescence and contributing to aging and chronic diseases. Understanding these factors can help you takepreventive stepsto maintain better health. Unlike conventionaltreatmentsthat only manage symptoms, senolytics aim to remove cause of many diseases by eliminate senescent cells.

DNA damage :-Our cells are continuously exposed to DNA-damaging agents like UV radiation, environmental pollutants, and toxins. When DNA damage overwhelms repair mechanisms, cells enter a senescent state to prevent the replication of faulty genetic material.

Oxidative stress :-Free radicals, unstable molecules that damage cells, accumulate from various sources, including diet, stress, and environmental exposure. This oxidative stress damagescellular components, prompting cells to cease division and become senescent.

Telomereshortening :-Telomeres, protective caps onchromosome ends, naturallyshorten as cells divide. Eventually, telomeres become too short to protect chromosomes, triggering a “stop” signal that leads to cellular senescence.

Inflammation :-Chronic inflammation fromconditions likeobesityor autoimmunedisorderscan overstimulate immune responses. This, in turn, can lead to cellular stress and push cells toward senescence.

Oncogenic activation :-Abnormal activation of certain genes can cause unregulated cellgrowth, risking cancer. To counter this, cells become senescent as a defense mechanism to suppress potential tumors.

Being aware and addition of drugs may delay onset of aging-related diseases, reducing environmental toxin exposure, managing inflammation, and supporting antioxidant-rich diets to slow the onset of cellular senescence.

II. Limitations and Challenges

Potential off-target toxicity: One of the most crucial issues in this sector is the safety of senolytic medications. These drugs are designed to remove senescent cells fromthe body, but sometimes they may also affect normal healthy cells.This is known as an off-target effect, and it can lead to unwanted side effects.For example, drugs that inhibit the BCL-2 protein family, such as Navitoclax, are effective at clearing senescent cells. However, they can also damage platelets in the blood by blocking the protein BCL-xL. This may cause a condition calledThrombocytopenia, where the number of platelets becomes very low. Because of this risk, the dose of such drugs must be carefully controlled.Some other senolytic drugs, like broad-acting kinase inhibitors or apoptosis-inducing agents, can also cause systemic toxicity if used for a long time or together with other medicines.

This problem is especially serious for older people, who are the main group that might receive these therapies. Elderly individuals often have multiple health conditions and take several medications at the same time, which increases the risk ofadverse drug reactions. To reducethese risks, scientists are working on improving the selectivity and delivery of senolyticdrugs. New approaches include targeted drug delivery methods such as tissue-specific prodrugs, antibody– drug conjugates, and nanoparticle-based systems. These strategies may help deliver the drug directly to senescent cells while protecting healthy tissues.

Limitedhumanclinicaltrials-
Althoughtherapiesthattarget cellularsenescencearereceivinga lot of attention and show promising results, there are still several scientific and clinical challenges that limit their wide use in medicine.

One ofthe maindifficulties is thatsenescentcells are not the same ineverytissue or condition. Senescence does not occur in a single uniform way.Instead, it can varydepending onthe type ofcell, the cause ofsenescence, the surrounding environment, and the ageofthe organism. Because ofthis variation, senescent cells maybehave

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differentlyin different tissuesofthe body. Somecells maydependondifferent survivalpathwaysorreleasedifferent inflammatoryfactors. Thismakesitdifficult forresearcherstodevelopasingledrugthatcaneffectivel ytarget alltypes of senescent cells in the body. As a result, the effectiveness of senolytic or senomorphic drugs may vary between patients or diseases. Another important limitation is the lack of reliable biomarkers that can accurately detect senescent cells inside the body without invasiveprocedures. Scientists commonly use markers such as p16INK4a, p21CIP1, SA-β- galactosidase, and γH2AX in laboratory studies to identify senescent cells. However, these markers are not completely specific to senescence and are difficult to measure in human tissues during clinical studies.

The lack of a uniform technique for calculating the total load of senescent cells in the body is another difficulty for researchers. This makes it challenging to track the effectiveness of a medication or identify the ideal dosage during clinical trials. Senescence is also not necessarily detrimental. Senescent cells can be helpful and transient in some circumstances, such as wound healing and tissue restoration. Therefore, removing these cells without proper understanding could interfere with normal biological processes. Scientists must carefully distinguish between beneficial temporary senescence and harmful chronic senescence that contributes to diseases.

Long-term safety is another concern. Since senolytic therapy is relatively new, the long-term effects of removing senescent cells from the body are not fully understood. Researchers must carefully study the potential consequences of prolonged treatment.

Finally, determining the optimal dosage and treatment schedule is another important challenge. Scientists need to find dosing strategies that maximize therapeutic benefits while minimizing harmful side effects.

Future Prespectives

In thecomingyears,researchon therapiesthattargetcellularsenescenceisexpectedtomo ve beyondbasicexperimentalstudiestowardtreatmentsth atcanbesafelyusedinhumans. The main goal is to enhance health span, or the amount of time spent in excellent health, in addition to improving life expectancy. Treatment approaches will also grow more sophisticated and accurate as researchers get a better understanding of how senescent cells behave in various tissues and situations.Previous methods mostly concentrated on removing the body's senescent cells. Future treatments, however, could adopt a more balanced strategy by either getting rid of dangerous senescent cells or cautiously controlling their activity as needed.

The creation of safer and more selective next-generation senolytic and senomorphic medications is one significant avenue. Researchers are working on creating medications that can target senescent cells in certain areas without harming healthy, normal cells. The creation of prodrugs that only become active within senescent cells due to their distinct metabolic traits is one potential strategy.

Another promising strategy is the use of antibody-based therapies that can recognize specific markers found on senescent cells. Proteins such as DPP4, uPAR, and Beta-2 microglobulin have been identified as possible markers present on certain senescent cells. Antibody–drug conjugates can attach to these markers and deliver drugs directly to the targeted cells, which helps protect healthy tissues from damage.

In addition,new drug deliverytechnologies are being exploredto improve the effectiveness of senescence-targetingtherapies. For example, nanoparticle-baseddrugdeliverysystems mayhelp carry medicines directly to specific organs or tissues. This approach can increasethe concentrationofthedrugatthetarget siteandreducesideeffectsinother partsofthebody. Such technologies may be particularlyuseful for reaching tissues that are difficult to treat, such as the brain or bone marrow.[171-172]

Modern research tools are also helping scientists better understand senescent cells. Advanced technologies like transcriptomics, proteomics, and metabolomics allow researchers to study the genes, proteins, and metabolic activities of cells in great detail. These techniques help scientists identify differences between various types of senescent cells in different tissues. By collecting this information, researchers are developing detailed maps or “atlases” of cellular senescence, which will guide the discovery of new biomarkers and therapeutic targets.

The use of artificial intelligence and machine learning is also becoming important in aging research. These technologies can analyze large biological datasets and help scientists identify patterns related to cellular senescence. As a result, researchers may be able to discover newpathways involved in aging and develop better methods for detecting senescent cells inthe human body.

Additionally, senescence and other biological

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processes including gene editing, autophagy control, and the gut microbiomeget investigated by researchers.In summary,thefutureof senescence-targetingtherapieslooksvery promising.Withcontinued advancesindrugdevelopment,biotechnology,andclinicalresearch,thesetherapiesmay advances in drug development, biotechnology, and clinical research, these therapies may eventually become effective tools for improving human health and reducing the burden of age- related diseases.However, careful research and responsible clinical testing will be essential toensure that these treatments are both safe and beneficial for patients.