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Understanding Cellular Senescence and Senotherapeutics for Nutri-geriatric Solutions

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Senescence is a hallmark of the natural ageing process across species. It is an irreversible arrest of the cells in a non-dividing state, restricting completion of cell cycle. Increased number of senescent cells is associated with declining health span. The switching between a normal cell to a senescent cell is governed by diverse factors, such as activation of DNA damage response, telomere attrition, raised redox imbalance etc. The senescent cells are detected through increased molecular markers of cell cycle arrest, chromatin remodeling indicators, lipofuscin, increased autophagic flux, and increase activity of senescence-associated ß-galactosidase. A hyper secretory inflammatory response referred as Senescence-Associated Secretory Phenotype (SASP) is also attained. SASP contributes to low grade chronic inflammation in elderly and contributes to pathophysiology of most geriatric diseases. Cellular senescence can be managed by inclusion of dietary entities that can clear senescent cells (senolytic action), rein the SASP response (senomorphic action) or facilitate re-entry to cell cycle (senoreversal). This scoping review presents the current understanding of cellular senescence activation and detection and compiles the findings from studies wherein dietary components - bioactive polysacchrides, peptides and proteins, fatty acids, lipids and probiotic formulations, that are reported to provide nutrition as well as confer an anti-senescent advantage.

Keywords: Anti- aging diet; Senescence-associated secretory phenotype; Senescent cells; Senolytics; Senoreversal agents; Senotherapeutics.

The natural process of aging is marked by a slow deterioration of body functioning over time. Ageing is coincident with phenomenon wide range of disorders or diseases that compromise the QoL of older people. It comprises of skin ailments, cardiovascular issues, and neurodegenerative diseases like Alzheimer's, compromised mobility due to loss of skeletal muscle mass and fraility, metabolic syndrome, obesity etc.[1] Cellular senescence, the cellular milieu of cell cycle arrest, in either the G1 or G2 phase stops the proliferation of damaged cells. It is a key hallmark of ageing due to exposure to sublethal exogenous stressors or activation of oncogenic pathway.[2] Physiologically, senescence has essential functions in tumor suppression, embryonic differentiation and development, wound healing and tissue regeneration, etc, but its role in onset of age-related diseases cannot be overlooked.[3] In fact, majority of age-related illness report a buildup of senescent cells with aberrant DNA, and a distinctive shift in the secretory composition known as – SASP, favoring inflammation associated secretory proteins, enzymes and signaling factors.[4]

Researchers are yet trying to decipher the dynamics between aging and senescence, with short-term buildup of senescent cells often being beneficial but long-term accumulation associated with disease incidence (Figure 1). An emerging category of pharmacological interventions targeting the pathological outcome of senescent cells are senotherapeutics. Senotherapeutics can be senomorphic (inhibiting the SASP responses), senolytics (selective elimination of senescent cells from diseases/aged tissue) or senoreversal agents that intend to switch back the "senescent" state to original state.[5] In 2019 the first successful clinical trial of dastanib and quercitin combination was published, wherein subjects with idiopathic pulmonary fibrosis exhibited improvement in physical performance after 9 doses of the combination over 3 weeks.[6] Since then several new senotherapeutic molecules have been tested in pre-clinical and clinical studies, the most recent being a phase one study of oral administration of dasatinib and that of quercetin in symptomatic patients with AD to evaluate the penetrance, safety and pharmacological efficiency. Notably, a decline in the senescence-related cytokines and chemokines as well as a raised level of Aâ42 in cerebrospinal fluid.[7] Understanding the role in cellular senescence in human physiology and diseases can aid the discovery and development of such novel senotherapeutics which can potentially ameliorate chronic diseases and extending lifespan/healthspan. The main objective of the present narrative review is to elucidate and discuss the present knowledge underscoring the molecular/environmental triggers of senescence in cells as we age, the SASP phenotype and the current technologies available to detect senescent cells. Hereafter we have compiled the current knowledge of various types of senotherapeutics based on differences in their ability to modulate the senescent state. A larger focus of the discussion are dietary senotherapeutics - namely carbohydrates, proteins, fats and lipids and small molecules of dietary origin, that have demonstrated pre-clinical and/or clinical benefits against the senescent cells buildup and pathological outcomes.

The main objective of this review is to elucidate and discuss the present knowledge underscoring the molecular/environmental triggers of senescence in cells as we age, as well as offer nutrigeriatric solutions *via* highlighting the benefits of dietary senotherapeutics.

Triggers of senescence

The phenomena of cellular senescence were initially reported in middle of 20th century by Hayflick and Moorhead as a proliferation limit in dividing somatic cells (normal human fetal fibroblasts) after multiple passaging and was called "replicative senescence" or "Hayflick limit".[8] Table 1 summarizes the differences between quiescent cells and senescent cells at different levels of morphology, function and molecular responses.

Cellular senescence, primarily categorized as replicative and stress-induced senescence is triggered by DNA damage, telomere shortening, organelle damage, oncogene activation, epigenetic changes, and the loss of tumor suppressor functions. Furthermore, cellular senescence inhibits proteasomal and lysosomal pathways by altering mitochondrial, lysosomal, and endoplasmic reticular function (Table 1).

The transit from normal cells into senescent phenotypic cells can be induced by one or several of the following molecular events [9]:

Telomere Attrition is a hallmark for replicative senescence, wherein the shelterin protein complex encasing the repetitive DNA sequence, located on chromosome termini progressively shorten with cell division, correlating with increasing number of cells switching to senescent state.[10] Interestingly ectopic expression of reverse transcriptase responsible for elongation of telomeres (telomerase enzyme) can counteract telomere shortening associated with progressive cell divisions and also bypass the switch to senescence. Shelterin complex consist of six proteins - TRF1, TRF2, POT1, RAP1, TIN2 and TPP1. The shelterin complex shelters the telomere-loop (t-loop) and thus prevents the single stranded chromosomal ends from triggering the DDR. In face of "end-replication problem" faced in telomere elongation with progressive cell divisions the components of shelterin complex destabilize and expose the t-loop eventually detected as a DSB, and triggers the DDR.[11]

Activation of DNA Damage Response: DDR is a complex signaling pathway for safeguarding genomic integrity, which can be activated by endogenous as well as exogenous

triggers. Endogenous (internal) molecular disturbances majorly known to trigger DDR are - formation of special DNA structures like secondary hairpin loops and G-quadruplexes, complication during replication and/or transcription (R-loops), topological stress, or deranged regulation of replicative proteins, imbalances in the cellular pool of deoxynucleotide phosphates, slowing/stalling of replication fork.[12] Exogenous (external) stressors include - exposure to radiation, genotoxic agents, or biological agents which increase ROS formation, or chemical modification of DNA .[12]

Senescence can be activated by different endogenous factors like telomere shortening, activation of oncogenes, dysfunctioning of mitochondria and/or endoplasmic reticulum and chromatin disruption.

The canonical pathway responsible for DDR activation is p53-p21 pathway, triggered by phosphorylation of p53 due to failure of inherent DNA repair mechanisms. Additionally, defects of epigenetic nature are initiated by the p16-retinoblastoma (Rb) pathway.[13]

Molecular initiators working via endogenous triggers are - bulky adducts leading to replication stress, inter-strand crosslinks, R-loop formation, transcription-associated recombination leading to DSB via transcription-coupled NER, and replication/transcription collisions leading to genomic instability.[14,15] To minimize these issues, replication and transcription are separated temporally and spatially during different cell cycle phases. Complexes like THO/TREX and THSC/TREX-2 aid in mRNA processing and nuclear export, preventing replication-transcription conflicts and R-loop formation.[16]

Oxidative Stress: It is an outcome of dysregulation in free radicals generation and the defenses of inherent cellular antioxidant. Oxidative stress is in fact theorized as an active contributor to cellular ageing and is theorized in the Oxidative Damage Theory.[17] ROS is primarily produced due to mitochondrial respiration, as a byproduct of ATP synthesis as oxygen can be partially reduced, and its derivatives such as superoxide anion etc. Excessive ROS, coupled with failing detox mechanisms, can damage cellular structural components (proteins, plasma membrane, carbohydrates) as well as functional multi-subunit structures - nucleic acids, enzymes etc.[18] This ROS-induced damage can trigger DDR by damaging mitochondrial DNA (mtDNA) leading to mitochondrial dysfunction which in turn can increase ROS production. This mtDNA damage in concert with decreased TERT activity and Ras, p53, p21, and p16 pathways can trigger the senescence phenotype. Additionally, ROS mediated p53 activation can also inhibit autophagy in senescent cells further aggravating the turnover of proteins and damaged organelles. These senescent cells then accumulate oxidized or carbonylated proteins along with lipid peroxidation products, and glycated protein products (lipofuscin). Interestingly ROS also induces production of miR-210 and miR-494, which can in turn inhibit autophagy and aggravate senescent phenotype.[19,20] Furthermore, redox imbalance in conjunction with mitochondrial functional disturbances can induced a pro-inflammation outset *via* activation of NF-êB signaling pathway, NLRP3 inflammasome, cGAS–STING pathway indicating at the close link between cellular senescence and inflammaging.[21] Another interesting link between failing oxidative defenses and increased senescent cell population is the decreased signaling via transcription factor Nrf2 a primary gatekeeper of cellular redox balance.[22] Thus, the buildup of ROS and its damage by-products, along with impaired antioxidant defenses and mitochondrial dysfunction, can initiate cellular stress responses that ultimately lead to cellular senescence.

Detection of senescent cells

Senescence is characterized by alterations in the cellular structural components, epigenetics and signaling pathways. A fail-safe recommendation to detect senescence in tissues is confirmation of at least three indicators giving a positive test – indicators of arrest of cell cycle progression, structural alterations such as increased vacuoles/ lysosomal vesicles, multinucleation, senescence-associated heterochromatic foci, flat appearance of cell and loss of lamin B1, indicators of DNA damage, redox imbalance, upregulated senescence associated secretory phenotype markers usually associated with inflammation such as cytokines or chemokines.[23,24] Table 2 summarizes the key markers used across studies to detect cellular senescence:

Markers of cell cycle arrest

Primary signaling cascades initiated by endogenous and exogenous stressors discussed

above activate the p53/p21-CIP1 and/or the p16/Rb pathway. The p53 pathway is activated during DDR, replicative senescence and during cellular milieu of redox imbalance, early in the cell cycle. The p16 pathway ensues during DDR response and replicative senescence, and is more often associated with maintenance of the senescent phenotype. [25,26] In either pathway, the final convergent point is Rb. Rb inactivation is critical for G1/S transition during the cell cycle via hyperphosphorylation, preventing complexing with the E2F and disrupting the Rb-E2F responsive genes' expression *via* transcriptional repression. This facilitates expression of genes needed for cell cycle progression e.g.cyclin E, Proliferating Cell Nuclear Antigen. On the other hand, in senescent cells, the hypo-phosphorylated Rb binds E2F preventing the transcription of replicative genes and hence halting the cell cycle and hence arresting the cells in senescence.[27,28]

These signaling markers can be detected with help of robust primers, probes, and antibodies, commercially available across commercial vendors. A key technical issue to be highlighted here is the gene expression studies of signaling mediators at transcriptional level (mRNA) or protein (western blot) level, uses constitutively expressed gene as control for quantitative analysis of gene expression. However, the expression of routinely used housekeeping genes is altered which can compromise the normalization of gene expression. Notable research backed housekeeping genes for use in senescence studies are - Tubulin Alpha 1a, Vinculin, L(3)Mbt-Like protein 2, Polycomb repressive complex1 subunit etc.[28]

In addition to molecular markers, indicators of cell cycle progression such as cellular proliferation or DNA replication assessment can also aid detection of senescence. Temporal assessment of cell number counts spectrophotometrically, or via automated cell counters and live cell microscopy can be used for detecting the cellular proliferation. Additionally, arrest in DNA synthesis can be detected via reduced incorporation of reagents like bromodeoxyuridine during the DNA replication in synthetic phase. Proliferation marker – nuclear protein Ki67 levels can also be measured via gene expression analysis or immunostaining of cells. During the S, G2, and M phases Ki-67 accumulates in the nucleus, while during G1 and G0 phases Ki-67 levels continuously degrade.[29]

SAHF biogenesis

SAHF are localized stretches of facultative heterochromatin that silence the expression of "progression of cell cycle" genes and direct a cell for exit from cell cycle. Thus, detection of SAHF is a direct indicator of cell cycle arrest stability. Largely, SAHF formation coincides with deactivating the E2F target genes (cell division and cell cycle progress to synthetic phase).[30] The formation of SAHF is dependent on activation of the Rb signaling pathway. The upregulation of E1A or silencing of p16INK4a can inhibit the formation of SAHF heterochromatin, interlinking Rb pathway with SAHF formation pathway.[31] Rb regulates the three-dimensional structure of heterochromatin and gene silencing in senescent cells, leading to the stability of the senescent state. SAHF chromatin reorganization and the combination of specific proteins like K9M-H3 and HP1 to E2F, leads to long-term suppression of E2F target genes, rendering cells insensitive to mitogenic signals. Consequently, E2F downstream genes are persistently downregulated in senescent cells, even when E2F-1 is introduced, indicating that SAHF contributes to the permanent arrest of cell proliferation.[32] Immunofluorescence based detection of macroH2A (a histone variant rich in SAHF), trimethylated lysine 9 of H3, HP-1 or inactivated p16INK4a are thus methods of choice for detecting SAHF formation.

Autophagy

Autophagy is a highly conserved and crucial process for cellular maintenance and clearance of senescent cells or compromised biomolecules and organelles, and eventually ageing. Errant autophagic pathways are a recognized hallmark of ageing.[33]

Macroautophagy is the principle autophagic pathway essential wherein cellular components (misfolded proteins, damaged organelles - mitochondria, in that case it is called mitophagy), and invading pathogens, are sequestered in autophagosomes. The autophagosomes merge with lysosomes, and the enclosed cellular components are degraded by the hydrolytic enzymes.[34, 35] Autophagy and cellular senescence are interconnected across multiple

signalling pathways and participant proteins.[36] Autophagic activity declines across multiple tissues during aging, for example in macrophages and other immune cells. This decline in autophagy is considered a hallmark of cellular senescence. Compromised autophagic pathways further pushes the aggregation of cellular damage, for example; aggregosomes, non-functional mitochondria, which contribute to the senescence process.

Furthermore, autophagy is closely linked to prevention of stem cell exhaustion, oncogenic transformation etc. The decline in autophagic activity during aging can contribute to these processes, exacerbating cellular senescence.[34,36] Additionally, autophagy is involved in reducing inflammatory responses, and its impairment during aging can lead to increased inflammation, another hallmark of cellular senescence. Interestingly, during aging, autophagosomes may not be able to fuse with lysosomes and build-up within the cell, which can serve as a marker of senescence. This accumulation can be monitored using various techniques, such as measuring the levels of the autophagy marker LC3-II (lipidated form of LC3) using microscopy, Western blotting, or flow cytometry. Flow cytometry with saponin permeabilization allows selective detection of membrane-bound LC3-II in immune cells.[37] Autophagic flux can be assessed by blocking this fusion with inhibitors like chloroquine or bafilomycin A1. This leads to the raised LC3-II levels, which is quantified over time. Additionally, tracer dyes (Cyto-ID) can be used to detect intracellular autophagic flux using flow cytometry.[37] Chaperone-mediated autophagy is the selective degradation of proteins containing a specific motif (KFERQ-like sequences) by lysosomes. CMA activity also declines with aging, impacting processes like T cell receptor (TCR) responses. CMA activity can be monitored using transgenic fluorescent protein reporters tagged with KFERQ sequences or by immunostaining for the CMA-associated proteins HSC70 and LAMP2A.[38] Several anti-aging interventions, such as calorie restriction or pharmacological interventions, converge on the induction of autophagy, suggesting that maintaining autophagic activity can delay cellular senescence and aging processes.

SA-âgal staining

Detection of â-galactosidase enzyme activity at acidic pH (pH 6.0), along with p16INK4a expression, is widely used as a biomarker for cellular senescence. While usually, â-galactosidase activity is localized to lysosomes and is active up to pH 4.5, senescent cells exhibit an accumulation of this enzyme, leading to activity being detected even at suboptimal pH of 6.0, and is classified as SA â-gal activity.[39]

The mechanistic action of SA-â-gal activity is attributed to escalate lysosomal biogenesis and altered composition during senescence, allowing â-galactosidase detection at non-acidic pH 6.0 in senescent cells. However, SA-â-gal as a senescence marker, is not entirely specific, as high cell confluency or serum starvation can also induce this activity independent of senescence.[39] Enhanced SA-â-gal is also closely linked with SASP.

Detection methods include histochemical staining on fixed tissues or flow cytometry with fluorogenic substrates like C12FDG. Detecting SA-â-gal (pH 6.0) requires lysosomal alkalinization, which may disrupt cellular physiology or necessitate fixation for sensitive cells. Due to its limitations, SA-â-gal in association with other senescence markers such as; p16INK4a, p21, SAHF, SASP, and SA-DDR assays should be used to ascertain the status of senescence in cells. In summary, SA-â-gal at pH 6.0 is the most rampantly cited senescence biomarker but should be interpreted alongside additional markers and functional assays.[40]

Lipofuscin detection

Lipofuscin of the ageing pigment is a yellow-brown complex accumulating in the lysosomes over the lifespan of post-mitotic cells. The composition includes oxidized cellular biomolecules and metal ions (iron, copper, zinc etc). Lipofuscin is resistant to proteolytic degradation due to its cross-linked structure and is also unaffected by exocytosis. Lipofuscin accumulation, a biological marker of replicative and ã-irradiation-induced senescence, and is highly colocalized SA-â-Gal activity. Although lipofuscin has natural fluorescence albeit with a wide emission spectrum (400-700nm), interfering with localization of the pigment. More reliable methods include use of Sudan black B dye (detecting lipids in lipofuscin), and periodic acid Schiff staining (detecting the carbohydrates)[41]. Additionally, chemical conjugates of Sudan Black B dye are

also reported for more sensitive detection via microscopy/flowcytometry, for example GLF16 is a modified Sudan-Black-B analog with fluorescent properties recently reported by Magkouta and coworkers, enabling detection of senescence using microscopy or cytometry.[42]

The SASP Response: secretory signatures

The SASP response is a hypersecretory phenotype in cells that have shifted to a senescent state, with secretions having autocrine as well as long distance paracrine impact. Analysis of the senescent cells' secretome unravels a dynamic composition of both soluble or insoluble and extracellular vesicle-related components. SASP response can exaggerate or diminish the absolute levels of these secreted molecular signals and contrasts significantly from the actively proliferating cells. Senescence messaging secretome is another name for SASP. The secretome can be triggered by stress, aging, DNA damage etc. The secretome consists of inflammatory cytokines, immune modulators (molecules that influence immune cell behavior), growth factors (proteins that regulate cell growth and repair), and proteases (enzymes that break down proteins) essentially culminating in a pro-inflammatory, pro-apoptotic, and pro-fibrotic milieu. Some common SASP factors common across cell types and different types of senescent inducing mechanisms (irradiation induced, UV-B induced, glyoxal induced) are IL-6, TNF-á, filamin B, cathepsin D, macrophage migration inhibitory factor, IL-7, IL-8.[23,24,43] The autocrine action of SASP reinforces the cell cycle arrest in the cellular self and the paracrine action works on neighboring cells. Physiologically SASP has a pivotal role in signaling for immune cells (natural killer cells or macrophages) to scavenge senescent cells. Additionally, SASP also operates during mammalian development, signaling for cellular-fate reprogramming. In adult life, SASP is also recognized to act in tissue repair for e.g. skin, liver injury etc.[23,44]

The regulation and variability of SASP are governed by multiple mechanisms at the transcriptional, translational, mRNA stability, and secretion levels, relying on positive feedback loops for signal amplification. Interestingly, consistent stimulation of DDR signaling is crucial for maintaining the senescent milieu and driving towards a SASP outset, whereas transient DDR is insufficient. Key transcriptional regulators of SASP expression include NF-êB and C/EBPâ. The DDR activates NF-êB *via* post-translational modifications of NEMO by the ATM kinase, leading to the transcription of SASP-related genes. cGAS, a cytosolic DNA sensor, connects DDR to SASP initiation by activating the STING-IRF3/NF-êB pathway in response to cytoplasmic DNA, often originating from micronuclei.[45] Moreover, MAPKs, especially p38, play a critical role in maintaining cell cycle arrest and activating NF-êB to promote SASP development. RBPs such as AUF1, HuR, and hnRNPA1 also significantly regulate SASP factor expression by influencing mRNA stability and translation.[46] Other factors, including the scavenger receptor CD36, transcription factor

Table 1. Difference between senescent cells and quiescent cells[8]

Features	Senescent Cells	Quiescent Cells
Cell cycle status	Mostly in the cell cycle's G1 or G2 phases	During the Go stage of the cell cycle
Triggering factors	Aging, DNA damage mutagens	Nutrient or growth factor deprivation
Reversibility	Reversible	Irreversible
Morphology	Enlarged and flattened	Retains normal cell morphology
Function	Metabolically active but do not proliferate	In a state of rest but viable
Chromatin changes	Forms dense heterochromatin bodies	Remain same
Cell marker	Increased expression of p16INK4a, p21. Altered morphology and lysosomal activity	Reduced DNA synthesis and metabolic activity, low expression of proliferation markers.
Role	Tissue repairs immune response but aging and age-related diseases.	Cells are ready to respond to signals and lead tissue regeneration.

GATA4, histone modifications, and various non-coding RNAs, houses the intricate regulation of multiple levels SASP.

The variability in the SASP response is influenced by the metabolic capacity of senescent cells. Notably, a dysregulation in the mitochondrial functional capacity is imperative for inducing senescence, induction of SASP outset and other senescence related cellular disturbances. For instance, depleting mitochondrial sirtuins such as SIRT3 and SIRT5 can trigger senescence and reduce the secretion of pro-inflammatory factors such as interleukin 1â, vascular endothelial growth factor etc in radiation-induced senescent human fibroblasts.[47] Mitochondrial dysfunction has a unique SASP profile that overlaps with but is also distinct from conventional SASP induced triggers as discussed above, and is known as Mitochondrial

Table 2. Biomarkers and detection methods of cellular senescence[26]

Identifying Trait of senescent cells	Marker	Detection Method
Blocked DNA synthesis	BrdU, EdU	Staining incorporation, IF
No proliferation	Ki67	Immunohistochemistry, Immunofluorosence
Triggered p16-pRB axis	p16INK4a	Western Blot, Immunohistochemistry, Immunofluorosence
Triggered p53-p21 axis	P21	Western Blot, Immunohistochemistry, Immunofluorosence
DDR	ãH2AX	Immunofluorosence
SAHF	DAPI/Hoechst 33342	Immunofluorosence
Telomere end shortening	Telomere	qPCR, Fluorescence in situ hybridization
ROS formation	Free radicals	Chemiluminescent oxygen detection reagents, fluorometry and flow cytometry

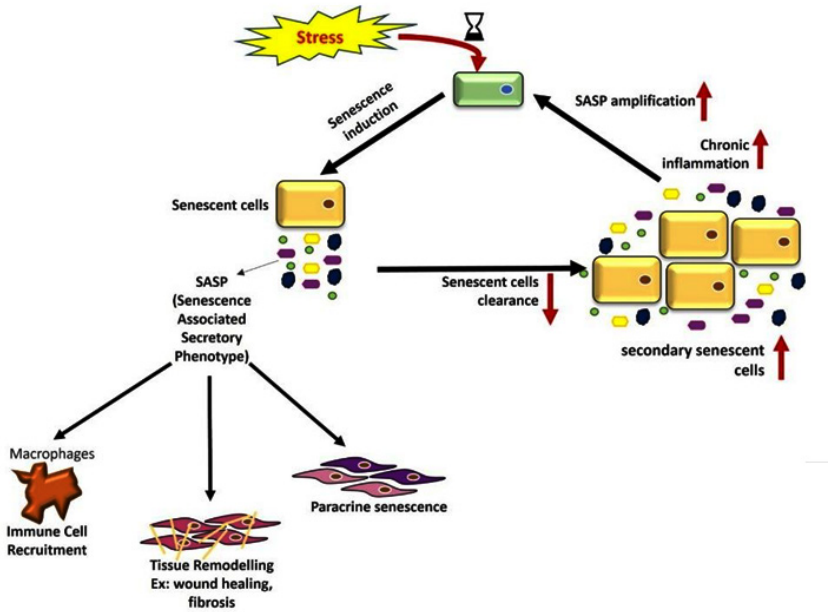

Fig. 1. Normal cells exposed to stressors for a long duration are triggered to a senescent state (cell cycle arrest), easily identified by SASP. Physiologically, senescence and SASP response are responsible for immune activation, immune cells' recruitment, tissue remodeling during wound healing and clearance of cells. But exaggerated senescence induction and SASP response leads to chronic inflammation and progression to disease.

Dysfunction-Associated Senescence. This offshoot of the senescence phenomena is driven by a lowered NAD+/NADH ratio, which negatively impacts NF-êB activity through the AMPK-p53 axis. Consequently, SIRT3 and SIRT5 emerge as potential targets for modulating the pro-inflammatory SASP. Furthermore, a decline in nicotinamide adenine dinucleotide levels could impair functioning of the PARP-1, an enzyme crucial for maintenance of mitochondrial genomic

Table 3. Phytocompounds and small molecules of plant origin with established senolytic/senomorphic activity and Indian Medicinal/Dietary Plant sources [https://neist.res.in/osadhi/index.html]

Senolytic/senomorphic phytocompound	Indian Plants
Quercetin	*Abelmoschus esculentus*
	Acer pictum
	Barleria dichotoma
	Daucus sativus
	Holigarna arnottiana
Naringenin	*Acacia farnesiana*
	Mazus pumilus
	Thespesia populinea
Gallic acids	*Abrus precatorius*
	Alocasia indica
	Eucalyptus hybrida
	Jurinea dolomiaea
	Rhodiola sacra
Ferulic acids	*Actaea cimicifuga*
Apigenin	*Acer laevigatum*
	Barleria cristata
	Colocasia esculenta
	Hedysarum triflorum
	Salvia viridis
Genistein	*Albizia procera*
	Canavalia gladiate
	Flemingia bracteate
	Phaseolus roxburghii
	Trifolium alexandrinum
Pterostilbene	*Anogeisus acuminata*
Carvacrol	*Achillea millefolium*
Epigallocatechin gallate	*Ceratolimon feei*
	Helianthemum glomeratum
	Limonium sinense
	Rhodiola heterodonta
	Thespesia populinea
Lycorine	*Crinum jagus*
	Hippeastrum puniceum
	Polianthes tuberosa
	Polyanthes tuberosa
Conophylline	*Tabernaemontana divaricata*
Piperlongumine	*Piper longum*
Fisetin	*Acacia catechu*
Curcumin	*Cucurma angustifolia*
Berberine	*Andira inermis*
Kaempferol	*Abrus precatorius*
Resveratrol	*Artocarpus chama*

integrity that requires this cofactor. The PARP-1/ NF-êB signaling pathway also promotes a tumor formation and metastasis associated with SASP in xenograft models, although the role of NAD+ levels in this context requires further investigation. [48] The diversity of the SASP response has been cataloged in SASP Atlas, an online comprehensive temporal and spatial proteomic database of SASP secretome, derived from different human primary cell types and triggers of senescence induction (genotoxic stress-induced, oncogene-induced, Atazanivir treatment). The platform can facilitate identification of distinct markers as well as markers elevated in all SASP responses.[49]

Senotherapeutics

The Sharpless group at School of Medicine, University of North Carolina pioneered the search for senotherapeutic agents in 2004.[50,51] They demonstrated a higher burden of senescent cells accompanied by raised expression of p16INK4a and Arf *in vivo* with ageing in rats. The pathology onset, senescent cell burden and expression of p16INK4a and Arf decreased with calories restriction (established anti-aging regime for lifespan extension in pre-clinical and clinical setting). By 2005, the team was working on two strategies to address the cellular burden of senescent cells, first involved creating fusion proteins with toxins to specifically destroy senescent cells. The second strategy screened human cell in dividing state vs. senescent state, for discovering chemicals that selectively kill senescent cells bypassing non-senescent ones. Thus, senotherapeutics emerged as a class of small molecules that specifically target only the senescent cell and their pathological molecular responses. As mentioned earlier senotherapeutics can be categorized as senomorphic, senolytics or senoreversal agents.[5,52] We briefly discuss the respective functional categories of senotherapeutics in the following sections, and also discuss the human dietary and natural sources of senotherapeutics:-

Senomorphic agents

Senomorphics are a class of molecules designed to modify the pathological molecular signatures of senescent cells without inducing

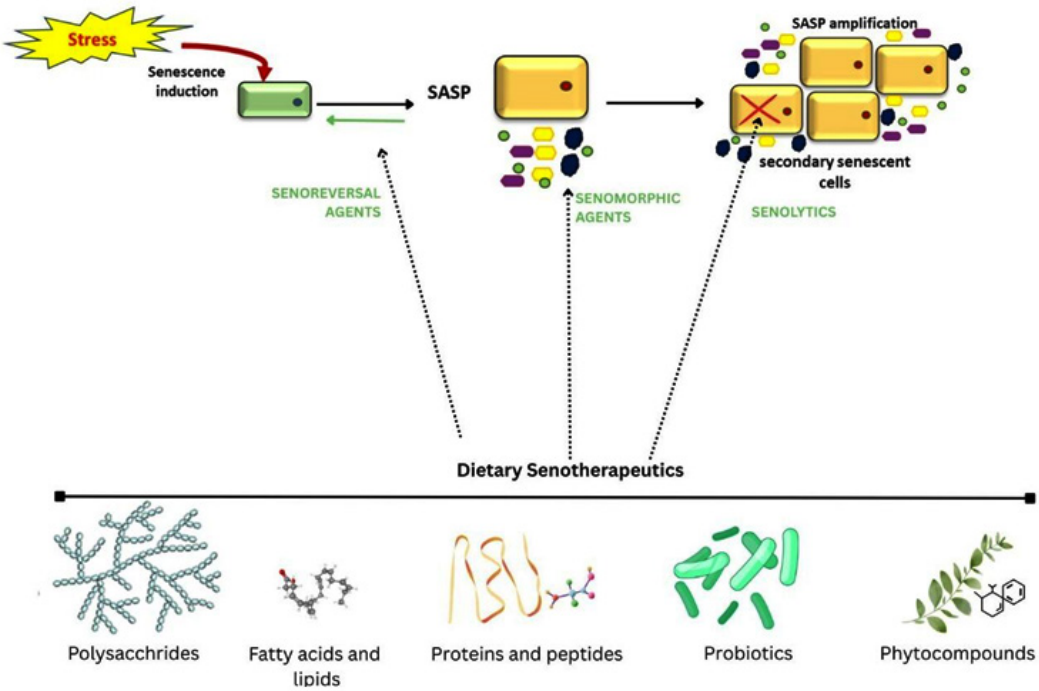

Fig. 2. Dietary Senotherapeutics can be of polysaccharide, lipids/fatty acids, protein extracts, probiotics or plant based small molecules. The senotherapeutics work via elimination of senescent cells (senolytics), controlling the SASP response (senomorphic) or reverting the senescent cells back to normal phenotype (senoreversal agents)

their death. Instead of eliminating these cells, senomorphics specifically target the SASP. By blocking or inhibiting the SASP components, senomorphics help mitigate inflammation and other detrimental processes associated with aging and tissue dysfunction. The known senomorphics target pathways downstream of p38MAPK, PI3k/Akt, mTOR, and JAK/STAT pathways, or through the transcriptional circuits of factors NF-êB, STAT3 etc. Indirect antibody mediated neutralization of cytokines/chemokines interleukin 1á, interleukin 8, interleukin 6 has also been noted.[23] Senomorphics hold promise for treating age-related diseases, especially with an underlying component of inflammaging such as cardiovascular diseases and neurodegenerative disorders.[53] Dietary bioactive molecules known to exhibit senomorphic action are Resveratrol, Kaempferol, Apigenin, and Epigallocatechin gallate, rutin, parthenolide, phloretin and curcumin. Synthetic senomorphic molecules include metformin, loperamide, cortisol among others.[54]

Senolytics

Senolytics are small molecules that specifically eliminates cells in the senescent state and hence reducing their accumulation during ageing and related diseases. Known senolytics work through varied mechanisms, but a unifying across mechanisms is exploiting the vulnerabilities of senescent cells, to which a normal cell is resistant or may cope with the pharmacological perturbation. The senolytic mechanisms include targeting the senescent cell's anti-apototic response (SCAP). Senescent cells develop resistance to apoptosis and have un/up-regulated pro-survival signals such as ephrins, PI3K etc. Senolytics can exploit this characteristic by precisely blocking the viability related signaling pathways in senescent cells, making them susceptible to apoptosis. The first line of senolytics discovered - dasatinib and quercetin, targeted the protective pro-survival signals in senescent cells.[55] Additional interventional molecules can be targeted to inhibit the anti-apoptotic molecular mediators through p53 (UBX0101), Bcl-2 (ABT-263 also known as navitoclax), Akt (alvespimycin and fisetin), PI3K (fisetin), FOXO4 (FOXO4-DRI) etc. Mechanisms routed through inhibition of Hsp 90 in oxidative stress induced senescence, as well as targeted delivery (to raised â-galactosidase activity in senescent cells) of galactose derivatives of cytotoxic agents (galactose-modified duocarmycin pro-drug), also are reported.[5]

Senoreversal agents

It is an advance approach that reprograms the senescent cells to reinstate the original dividing state or reversing the arrest on the cell cycle. The earliest reports on senoreversal came from An and co-workers wherein *in silico* prediction based on molecular regulatory network of cellular senescence, PDK-1 inhibition was tested in human dermal fibroblasts using pharmacological inhibitors. The inhibition of PDK1 suppressed mTOR and nuclear factor êB, alleviating the proliferative arrest and SA-â-gal–positive cell population declined from >80% to <40%. Clinical evidence for PDK1 inhibition using kaempferol tetrasaccharide a natural senotherapeutic was put forth by Kim and co-workers.[56,57] A groundbreaking study conducted by Bi and co-workers recently, reported the senoreversal capacity of human embryonic stem cell-derived exosomes, restoring the senescent cells proliferation ability, largely due microRNA-302b (enriched in human embryonic stem cell-derived exosomes) *in vitro* as well as in aging mice.[58] Senoreversal molecules are known in limited capacity and a larger focus is on senomorphics senolytics. In fact in light of the heterogenous nature of senescent cells and triggers thereof, senotherapeutic molecules have been shown to have dual action of senolysis as well as senomorphic.[55] Also, treatment regimens with senolytics are aggressive, whereas senopmorphic agents merely suppress the pathological SASP, and are deemed safer in long term studies.[59]

Dietary sources of senotherapeutics

Dasatinib and quercetin cocktail is the most clinically evaluated senotherapeutic intervention, but not without adverse effects. In a pilot trial of dasatinib and quercetin treatment (100mg/1250 mg) regime for idiopathic pulmonary fibrosis, a higher incidence of non-serious adverse events (cough, shortening of breath, nausea, general feeling of fatigue, weakness and sleep disturbance, depressive behavior etc) was reported against the placebo group.[60] Additionally, the thrombocytopenia, and minor steatosis were also reported in other studies.[61] The human dietary components - carbohydrates, proteins, fats and lipids, vitamins, small molecules of plant/

animal origin , and probiotics, have stand alone or in concerted action have been demonstrated to modulate the burden of cellular senescence.[62] We herein discuss the dietary senotherapeutics that can be easily, safely and cost-effectively included in geriatric diet regimes, offering long term benefits in preserving health span alongside lifespan [Figure 2].

Carbohydrates and derivatives as senotherapeutics

Carbohydrates are the foremost energy source. Excess consumption of carbohydrates and deranged metabolism/utilization of carbohydrates is positively linked with incidence of chronic disorders - obesity, insulin resistance progressing to diabetes.[63] Notably, diets enriched with glucose/ fructose are used to simulate animal models of accelerated ageing and at the same time restriction in calories originating from reduced carbohydrate intake improves metabolic risk markers of obesity, and metabolic syndrome.[64]

Nevertheless, complex carbohydrates and derivatives have demonstrated a positive impact on reigning cellular senescence at molecular level and may aid expansion of healthspan. Several research groups reported polysacchrides derived from *Astragalus membranaceus*, also known as Mongolian milkvetch, aids recovery of hepatocyte senescence via phosphorylation of AMPK and blockade of mTOR pathway in L02, Huh7, and LM3 cell lines as well as 15-month-old female C57BL/6 mice. *Astragalus membranaceus* polysacchrides when tested in rat aortic endothelial cells treated with high glucose, significant decrease was observed in the cell count positive for SA-â-Gal activity, expression of biomarkers p16, p21, and p53 and inflammasome activation.[65] *Angelica sinensis*, a prominent herb in traditional Chinese medicine, is the source of angelica polysaccharide. The *Angelica* polysacchride has demonstrated anti-cellular senescence and potent antioxidant properties across cellular models - haematopoietic cells, endothelial progenitor cells, and in murine animal model of chemically induced accelerated aging. The *Angelica* polysacchride, administered to mice for 42 days via intraperitoneal route, alleviated redox imbalance, decreased advanced glycation end products' titre systemically, decreased count of SA-â-Gal positive cells as well the expression of *ã*-H2A.X culminating via the Wnt/*â*-catenin signaling pathway.[66,67] Polysaccharides derived from *Lycium barbarum*, *Bletilla striata*, and *Rehmannia glutinous* were demonstrated to control the onset of senescence in *C. elegans* via DAF-16 transcriptional activation downstream of insulin/insukin like growth factor signaling pathway-1.[68,69] Another interesting source of anti-senesence polysacchrides are marine fucoidan, demonstrated to rescue p-cresol mediated shift to senescence in stem cells (p-cresol is a uremic toxin responsible to kidney damage) can reinstate endothelial cells from cellular senescence, and enhance their survival.[70] Concurrently, in light of the emerging anti-senescent activity of poly-sacchrides and carbohydrates, an inclusion of the discussed bioactive polysaccharides alone or their source herb in geriatric dietary regime could prove beneficial, and should be pursued for innovations in nutraceuticals.

Dietary proteins and peptides as senotherapeutics

Proteins are largely associated with structural, signaling and catalytic activity across prokaryotes and eukaryotes. For a healthy human adult 2 g per kg body weight of protein consumption is recommended. Proteins in combination with carbohydrates form the major portion of human diet, and hence the recommended carbohydrate to protein ratio for heathy ageing is 10:1.[71] At the cellular level, imbalance in proteostasis (homeostatic mechanisms to maintain a balanced and functional proteome) is directly linked to onset of senescence and decline in lifespan of the cell/organism. Notably, protein homeostasis is compromised in senescent cells and this aiding the re-establishment of Proteostasis, critical to offset senescence.[72,73] Categorically, several peptide and protein hydrolystaes have been now reported to have senotherapeutic potential. Notably protein hydrolyzate from *Angelica sinensis* led to identification of *A. sinensis* peptides (AsiPeps) <3kDa and <20 amino acids in length, reduced the systemic reactive oxygen species levels, raised enzymatic antioxidant defences and controlled oxidative damage to structural lipids in *C. elegans* worms undergoing paraquat induced senescence, eventually culminating into increased lifespan.[74] Another recent example is of a 13-amino acid long peptide of soybean origin - Soymetide (MITLAIPVNKPGR). Soymetide has been demonstrated to delimit the senescence

associated markers (p53, p21 and p16) as well as inflammatory chemokines and cytokines in the brain tissue of doxorubicin-induced senescent mice C57BL/6 male mice *via* the Wnt/â-catenin signaling pathway. The senotherapeutic efficacy of soymetide was at par with that of standard senolytic combination of dasatinib and quercetin, and was effective in preserving the cognitive outcomes.[75] Walnut derived protein hydrolysates and their low-molecular-weight components has shown senomorphic potential in AD mice model, notable outcomes depicted were balance pro-inflammatory factors (cytokines and chemokines), autophagic flux, and redox imbalance.[76] A dipeptide identified in alkalase potato-protein hydrolysates administration in combination with moderate training in old high fat diet induced SAMP8 mouse model could decrease the burden of senescent cells and improve physiological functioning via the pAMPK/ SIRT1/ PGC-1á/ pFOXO3 pathway.[77] Senomorphic action has also been observed in peptides P1 (VLVLDTDYKK) and P2 (VGINYWLAHK) derived from whey hydrolysates in a model of oxidative stress induced senescence in human dermal fibroblasts.[78] However, contradictory studies also exist wherein protein-rich diets lead to declined systemic NAD+ levels, raised SASP and hence accelerated senescence in animals and in humans.[79,80] Together, the conflict of high protein intake *vs* low protein intake must be assessed on the potential impact on senesence triggering mechanisms, and the identified bioactive senotherapeutic peptides can be carefully combined with bioactive carbohydrates to confer a multipronged benefit.

Fats and lipids as senotherapeutics

Fatty acids, especially, essential fatty acids - omega-3 and omega-6 fatty acids, are recognized to have critical role in healthy aging.[81] Daily inclusion of these essential lipids in geriatric diet is proven to benefit in inflammaging, sarcopenia and osteopenia, type II diabetes, cardio-vascular health and most other age related illness.[82] As modulators of senescence the role of lipids and fatty acids is only emerging now, with links indicated with triacylglycerol and diacylglycerol, phospholipids, poly- and mono-unsaturated fatty acids as well as sphingolipids.[83] Investigation on sphingolipids dominate the literature interlinking lipids' role in regulating senescence across cell types. Ceramide has been linked to induction of growth arrest and replicative senescence in cell types - bone derived mesenchymal stem cells, endothelial cells.[84]

S1P, the functional adversary of ceramide,[85] is a pro-proliferation lipid and intracellularly decreased S1P levels are associated with accelerated senescence. However, co-treatment of cells with S1P and fumonisin B1 (decreases intracellular ceramide levels by inhibiting ceramide synthase) can reverse the signalling switch to senescent phenotype.[86] Additionally, S1P binding to human telomerase reverse transcriptase can mimic the enzyme's phosphorylation mediated stabilization and hence control the senescence-associated-telomere-damages.[87] Conversely, S1P signaling via S1P receptor increases pro-senescent signaling in endothelial cells accompanied with a pro-inflammatory chemokines/cytokines and lipid mediators in ECs SASP response.[68] Overall, senescent cells have a deranged lipid metabolism globally, remodeling the cellular membranes and triggering the SASP phenotype, as studied by Lizardo and co-workers in Senescent BJ fibroblasts, with a predominance of nineteen polyunsaturated fatty acids triacyl glycerols moieties. The response was governed by a CD36-mediated fatty acid uptake, being diverted to glycerolipid synthesis as a means to cope with lipotoxicity associated with replicative senescence.[88]

A groundbreaking observation was also reported by Fafián-Labora and co-workers during their investigations in mouse hepatic stellate cells and human primary fibroblasts, and in aged mouse hepatic tissues, the fatty acid synthase activity increases upon onset of senescence.[89] And hence several clinical and preclinical studies endorse dietary inclusion of omega 3/6 fatty acids in geriatric diets leading to favorable outcomes. For instance, Chan and co-workers exhibited that consumption of n-3 polyunsaturated fatty acids, of marine origin, in subjects who had undergone renal transplant, controlled the triggering of cellular senescence, and coincident SASP response. Consumption of marine n-3 polyunsaturated fatty acids, in comparison to consumption of olive oil as placebo, for forty four weeks controlled systemic levels of IL-1á, MIP-1á, MMP-1, MMP-13 amongst other inflammatory etc, and hence aiding in successful recovery of transplant patients.[90] The anti-senescence effects of marine

docosahexaenoic acid and eicosapentaenoic acid have also been identified and represented in cohort of patients with coronary artery disease, wherein a decrease in replicative senescence was observed in leukocytes via preservation of telomere ends.[91] This phenomena was recapitulated in vitro in endothelial cells wherein treatment with docosahexaenoic acid and eicosapentaenoic acid (from fish oil), attenuated DDR [ã-H2AX foci formation decreased by nearly 50%] linked with cellular senescence and augmented the inherent anti-oxidant defences via NRF2.[92] Conclusively, lipids and fatty acids are only emerging as modulators of senescent pathways and detailed understanding of lipidomic responses of senescent cells will aid our understanding to use lipid based senolytic interventions that can be a part of geriatric diet.

Probiotics as senotherapeutics

Consumption of probiotics has beneficial effects across human health and disease pathology - probiotics can regulate immune effector responses, nutrition uptake from gut and its metabolism, brain development and cognition, progression and success of therapy in cancer, inflammatory bowel disease, Alzheimer's, diabetes etc.[93] As the ingested dietary components come in contact first with the gut microbiota and are substrates for several microbe mediated biotransformation, the composition of beneficial microbiota in the gut can very efficiently modulate the molecular and hence physiological outcomes of dietary molecules.[92] The ageing population's gut microbiome signatures indicate a loss of microbial diversity, linked to age-related decline in digestion and metabolic capacity, immunity, and general physiological functioning, potentially impacting healthspan as well as lifespan of an individual.[94] Dysbiotic gut, a frequent occurrence in aged populations, is an inflammatory microenvironment that can exaggerate the SASP response, as demonstrated in a mouse model of dysbiosis. The animals had raised levels of deoxycholic acid, exacerbating the SASP response in hepatic stellate cells, further exaggerating the systemic inflammation and development of hepatocellular carcinoma.[95] Thus, probiotic formulations as a part of geriatric diet can be positioned as senomorphics due to their ability to modulate the SASP and reduce systemic inflammation. For instance, the study by Jeong and co-workers exhibited the efficacy of administration of probiotic *Lactobacillus* strain, to aged rats for eight weeks significantly controlling the inflammaging response, systemic oxidative stress and controlled the incidence of age-related colitis.[96] Fang and co-workers developed a probiotic formulation of *Lactobacillus* and *Bifidobacterium* species derived from centenarian population. The formulation when administered to the SAMP 8 mouse model exhibited positive outcomes in cognitive and behavioral performance, neuroinflammation, gut inflammation, and composition of the gut microbiota.[97] All together, these finding endorse the discovery and efficacy testing of "gerobiotics" for inclusion in either geriatric dietary regimes or as nutraceutical formulations to be used in supplementation with wholesome anti-senescent diets.

Small molecules and phytocompounds as senotherapeutics

A large volume of literature exists wherein plant derived small molecules from diverse classes - polyphenols, saponins, alkaloids etc have been reported to have senomorphic or senolytic activity. The authors intended to cover the dietary constituent other than bioactive phytocompounds and hence the readership can refer to detailed reviews on the theme elsewhere.[5,59] Table 1 however reports a compilation of Indian plants and herbs where the much-investigated senolytic/senomorphic compound is a part of the composition. These Indian plants can be included in a bioprospecting study to unveil novel senotherapeutic compounds.

CONCLUSION

As our understanding of molecular and cellular aspects of ageing evolves, one can expect more targeted, effective and holistic interventions to prolong the human health span. Cellular senescence and its implications on human health, especially in geriatric diseases is well established. But it is only now that we have identified the triggers responsible for switching from a normal cell type to an arrested pro-inflammatory cell (senescent cell) and the characteristics of the senescent phenotype. Senotherapeutics are an emergent class of small molecules, specifically targeted to remove senescent cells or control the SASP mediated pathological damage. The current most successful senotherapeutic combination is dasatinib and

quercetin, under investigation in several clinical trials, however we reviewed the current state of the art of senotherapeutic entities that can be a part of everyday diet. Bioactive polysacchrides, peptides and proteins, fatty acids, lipids can exhibit senolytic capacity and control the buildup of senescent cells as we age. Probiotic formulation, standalone microorganisms or in combination, can confer senomorphic advantage by countering/ controlling the SASP response. Conclusively, the authors endorse mechanistic investigation into dietary entities that can aid control the age-related burden of senescent cells and also provide nutrition. The dietary senotherapeutics can be included in scientifically curated geriatric diets or formulated into targeted nutraceuticals for elderly.

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Not applicable.

Authors' contribution

Sonam Chawla conceptualized and wrote the first and the final of the present manuscript; Sanjukta Bhattacharya performed literature survey and prepared the figures and tables; Aaysha Gupta contributed to editing the manuscript and finalizing the present draft.

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