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Senolytics and Dietary Phytochemicals: Exploring Anti-Aging Strategies and Mechanisms in Aging and Disease

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ABSTRACT

Senolytic drugs (Anti-aging drugs) selectively eliminate senescent cells (SC), which are resistant to apoptosis and have up-regulated anti-apoptotic pathways that protect them from their inflammatory senescence-associated secretory phenotype (SASP). These drugs temporarily disable these pathways, inducing apoptosis in SCs with a tissue-destructive SASP. Initially identified through hypothesis-driven research, senolytics like Dasatinib, Quercetin, Fisetin, and Navitoclax have shown in preclinical models to delay, prevent, or alleviate frailty, cancers, and various disorders as well as complications from organ transplantation. Senolytics like Azithromycin and Quercetin, which have anti-aging properties, are proposed as potential treatments. Since 2015, several senolytics have progressed to clinical trials. Recent studies link chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) to accelerated aging mechanisms, including cellular senescence. COPD's diversity, with its range of phenotypes, implies that lung aging may play varying roles in different phenotypes, complicating the identification of COPD patients who might benefit from senolytics. Preclinical evidence suggests senolytics reduce all-cause mortality, enhance physical function and resilience, and alleviate diseases across various organs, even in elderly patients. Diet provides energy, nutrition, and enjoyment. Studies show that major dietary components regulate aging and longevity. The potential for other dietary ingredients to prevent aging and extend longevity is intriguing. Recent findings suggest that certain plant-based ingredients can extend longevity by regulating metabolism, targeting TRP channels, reactive oxygen species (ROS), promoting mitophagy, influencing senescence pathways, and modulating circadian rhythms. Understanding these may help develop interventions for aging and related diseases. Calorie restriction and dietary manipulations that reduce ROS and inflammation while promoting autophagy can extend lifespan in model organisms. Some phytochemicals also extend lifespan in animals. This review examines the role of senescent cells in aging and disease, methods for discovering and refining senotherapeutics, and the status of senolytic preclinical and clinical trials and highlights anti-aging phytochemicals studied in cells, animals, and humans, exploring their cellular and molecular mechanisms.

Keywords: Senolytics, Senescent cells, Apoptosis, COPD, COVID-19, IPF, Senotherapeutics, ROS, Diet, Aging, TRP channels, Mitophagy.

INTRODUCTION

Senescence is the result of a signalling pathway that is triggered in stressed cells to stop damaged cells from proliferating. Preclinical data indicate that senolytics (Antiaging Drugs) alleviate disease in numerous organs, improve physical function and resilience, and suppress all causes of mortality, even if administered to the aged. Here, we review the evidence that Sncs drive aging and disease, the approaches to identify and optimize senotherapeutics, and the status of preclinical and clinical testing of senolytics.[1] Early pilot trials of senolytics suggest they decrease senescent cells, reduce inflammation, and alleviate frailty in humans. Clinical trials for diabetes, idiopathic pulmonary fibrosis,[10] Alzheimer's disease, COVID-19,[8] osteoarthritis, osteoporosis,[9] eye diseases and bone marrow transplant and childhood cancer survivors are underway or beginning. Until such studies are done, it is too early for senolytics to be used outside of clinical trials.[2] Since 2015, several senolytics went from identification to clinical trial. Preclinical evidence suggests that senolytics, even when given to elderly patients, reduce all causes of death, enhance physical function and resilience, and relieve disease in a variety of organs. Here, we examine the data supporting the theory that Sncs cause ageing and disease, the methods used to find and enhance senotherapeutics, and the current state of senolytic preclinical and clinical trials.[1] With chronic diseases accounting for most global morbidity, mortality, and health care costs, old age is the biggest risk factor.[3] The majority of malignancies, osteoporosis, arthritis, blindness, strokes, dementias, chronic lung diseases, diabetes, renal failure, and neurological diseases are among these chronic illnesses. Individuals who are older are also more susceptible to physical resilience decline and geriatric disorders. Frailty, sarcopenia, immobility, falls, depression, mild cognitive impairment, incontinence, metabolic syndrome, and weight loss are among the geriatric syndromes. Impaired response to immunisation and delayed recovery from myocardial infarction, stroke, trauma, infection, chemotherapy, surgery, or fractures are examples of decreased physical resilience. Elderly people frequently have combinations of these disorders, and the frequency of multimorbidity—the occurrence of three or more conditions at once—increases exponentially in the third tertile of life.[4] The possible benefits of healing any one age-related illness are complicated by the existence of multimorbidity.[5] The geroscience hypothesis, which holds that therapeutically targeting fundamental ageing mechanisms will successfully influence various chronic diseases since these diseases all share the same underlying mechanism, was prompted by the realisation that old age is the highest risk factor for most chronic diseases.[3]

Treating underlying ageing mechanisms instead of individual diseases offers enormous potential health and financial benefits.[6] In fact, according to one estimate, if we were to delay the ageing process by 2% instead of doing nothing or finding a cure for cancer or heart disease, we would save $7.1 trillion over the next 40 years and have 10 million extra older Americans who would be healthy rather than crippled.[1] Senolytics can be used to eliminate SC selectively because it takes weeks for SC to reaccumulate. Senolytics delay, prevent, or mitigate frailty, malignancies, and disorders of the heart, brain, liver, kidney, musculoskeletal system, lung, eyes, haematological system, metabolism, and skin. They also mitigate the problems of radiation, organ transplantation, and cancer treatment in preclinical animals. Senolytics have a wide range of potential applications; in preclinical studies, they have been shown to potentially alleviate over 40 conditions, providing a new avenue for the treatment of age-related dysfunction and diseases. This is to be expected for agents that target the fundamental ageing mechanisms that are "root cause" contributors to multiple disorders.[7] Clinical trials are being conducted to investigate senolytic medicines as a proof of concept. Because it is not practical to utilise long-term outcomes like lifespan or healthspan,

new clinical trial paradigms are being created to evaluate senolytics and other treatments that target core ageing pathways. These medications have been shown to lower inflammation, stop cardiovascular disease, and delay the functional deterioration of specific organs in people. Furthermore, certain components of cell metabolism, proliferation, angioneogenesis, and apoptosis are disrupted by possible anti-aging pharmaceutical drugs, which also suppress cancerogenesis.[11]

Table 1: Senotherapeutics reported to date and methods of discovery [1]

First-generation senolytics: Hypothesis-driven, mechanism-based discovery: **Agent**
Dasatinib
Quercetin
Luteolin
Curcumin
Curcumin analog EF24
Navitoclax (ABT263)
A1331852
A1155463
Geldanamycin, tanespimycin, alvespimycin, and other HSP90 inhibitors
Piperlongumine
FOXO4-related peptide
Nutlin3a [although Nutlin3a can also cause senescence (87)]
Cardiac glycosides such as ouabain, proscillaridin A, and digoxin
Aspirin
Second-generation senolytics: Traditional and other drug discovery methods
High-throughput compound library screens
Vaccines
Toxin-loaded nanoparticles preferentially lysed by Sncs
Immunomodulators
Cell-based therapies

CLINICAL TRIAL STRATEGIES [11]

To evaluate senolytics or other drugs that target basic ageing processes, new approaches to clinical trials will be required. It is not feasible to examine certain outcomes in people, such as impacts on median or maximum longevity. The geroscience hypothesis states that a potential medication should address a variety of chronic illnesses, geriatric syndromes, and age-related loss of physiological resiliencies if it tackles basic ageing processes.[12][13][14] Thus, the following are examples of possible clinical study scenarios.

1. Simultaneous alleviation of multiple comorbidities. In individuals with multimorbidity, which is common in older adults, candidate senolytics should alleviate more than one pathology, such as glucose intolerance, mild cognitive impairment, joint pain due to osteoarthritis, systolic hypertension, or low carotid flow. Alternatively, these drugs should delay the onset of a second age-related disorder

in individuals who already have one disorder, like the design of the Targeting Aging with Metformin trial for testing the effect of metformin on fundamental aging processes.[16]

2. Alleviation of potentially fatal diseases. Several diseases for which there is no effective treatment are related to accumulation of senescent cells. These include idiopathic pulmonary fibrosis and primary sclerosing cholangitis.[17] Senolytic agents hold promise as treatments for these conditions. In these examples, the potential benefits of treatment are likely to outweigh the risk of side effects.
3. Treatment of conditions with localized senescent cell accumulation. Several disorders, including osteoarthritis,10 idiopathic pulmonary fibrosis,[18] and retinopathies, are associated with localized accumulation of senescent cells. This offers the opportunity to administer senolytics by injection or aerosol, which will reduce the risk of side effects.
4. Treatment of accelerated aging-like states. Senolytics or other agents that target basic aging processes may be effective in treating conditions associated with accelerated aging-like phenotypes, including those induced by chemotherapy related to bone marrow transplantation or treatment of childhood cancers, human immunodeficiency infection, obesity, or genetic progeroid syndromes. Short-term trials examining outcomes such as reduction of multimorbidity, frailty, or rate of functional decline may hold promise. [12]
5. Augmenting physiological resilience. Resilience, or capacity to recover after a stress such as surgery, chemotherapy, radiation, pneumonia, or a myocardial infarction, declines with aging. Lack of resilience also underlies such conditions as poor immune response to influenza vaccination or deceased ability to exercise with aging. Loss of resilience occurs before the onset of frailty and other conditions that are visible even in the absence of stress. Thus, testing if drugs that target fundamental aging processes enhance recovery following stressful medical interventions or acute injury might be an informative clinical trial strategy. For example, such trials could be based on the observations that senolytics reduce adverse consequences of bleomycin-induced pulmonary injury and radiation-induced injury in mice. A drug related to rapamycin, an agent that inhibits the SASP, increased immune responses to influenza vaccination in elderly community living subjects.[19]
6. Alleviation of frailty. Targeting senescent cells, even in late life in rodents, appears to reduce immobility, weakness, fat tissue loss, and other parameters associated with frailty. Senolytics may be tested in short-term clinical trials that include older adults with a moderate degree of frailty to determine whether strength, gait, body weight, or other relevant parameters improve. [20]

SENOLYTIC THERAPIES

SENESCENCE AND IPF

There is evidence to suggest that senescent cells can exert strong impacts on neighbouring cells via their SASP, which can ultimately lead to functional lung degeneration.[22] On the other hand, there is evidence that elimination of senescent epithelial cells stabilizes the epithelial cell phenotype and lowers fibrotic markers in experimental and human lung fibrosis tissue and primary cells. In vitro bleomycin-induced fibroblast senescence has a proinflammatory phenotype that is mitigated by the administration of the senolytic **quercetin**.[23]

In rats with bleomycin-induced pulmonary fibrosis, quercetin's inhibitory effects were compared to those of vitamin E. The results showed that quercetin had greater antifibrotic activity than vitamin E because it significantly reduced the levels of inflammatory fibrotic factors like TNF-α, PDGF-β, and IL-13 while increasing the level of the antifibrotic factor interferon-γ. [24] Quercetin also reduced the amount of

collagen deposition, antioxidant-oxidant imbalance, and MMP-7 activity that were brought on by bleomycin in lung tissues. Following bleomycin injury, dasatinib and quercetin together improve lung function and markers of fibrotic illness.[25]

SENESCENCE AND COPD

There are many similarities between the aging process in the lungs and COPD, and many of the hallmarks of aging are present in COPD, suggesting that accelerated aging may be a pathogenic mechanism in COPD.[26] Telomere shortening, which may be aresult of increased oxidative stress, greater mitochondrial ROS generation, which is directly induced by cigarette smoke exposure or through ineffective clearance of dysfunctional mitochondria through mitophagy (selective degradation of damaged mitochondria), and epigenetic changes, including DNA methylation, histone modifications, and altered expression of noncodingRNA molecules, might all contribute to the genomic instabilityobserved in the lungs of patients with COPD.[27] Dysfunction inthese pathways could contribute to the increased number of senescent cells observed in the lungs of patients with COPD.

It is presumable that senescent cells participate to COPD pathogenesis through impaired lung regeneration (stem cellexhaustion), an increased susceptibility to apoptosis, and the release of SASP components (altered intracellular communication). The numbers of inflammatory cells and the production of proinflammatory cytokines and chemokines are increased in the lungs of patients with COPD, perhaps exacerbated by the enhanced basal inflammation that is a component of 'inflammaging'.[27]

Recently, it has been suggested that HDAC2, which is a critical determinant of chromatin remodelling and is reduced because of oxidative stress-mediated DNA damage and impaired repair, is a key player regulating cigarette smoke– induced DNA damage, inflammatory response, and cellular senescence leading to COPD/emphysema.[28]

ANTISENESCENT THERAPY

In the past few years, it has become clear that senescent cells have distinct molecular vulnerabilities. Specific agents called senolytic compounds, which are pharmacological agents that preferentially kill senescent over non-senescent cells, have the potential to target these different molecular foci.[29]

Experimental data have demonstrated that selective elimination of senescent cells might prevent or delay age-related functional impairments and extend health span. Furthermore, depletion of senescent cells presents a potential therapeutic option for the treatment of several chronic diseases, including those of the aging lung.

Antisenescent strategies consist of the selective elimination of senescent cells, referred to as senolysis, immune-mediated senescent cell clearance, and SASP neutralization. Senolysis is the most promising approach because permanent removal of senescent cells leads to a long-lasting abolishment of detrimental SASP components, and because, once a senescent cell is eliminated, there is no risk of tumorigenic 'escape' from senescence, which may be possible if senescent cells are permitted to stay indefinitely.[30]

SENOLYTIC AGENTS

Identification of small molecules that act by inhibiting prosurvival and antiapoptotic proteins that are specifically upregulated in senescent cells, with the potential to selectively induce death of senescent cells seems to be a promising therapeutic approach in antiaging medicine. The pharmaceutical agents that target these senescent cells are dependent on senescence-specific vulnerabilities compared with normal dividing

or differentiated cells. It has been suggested that treatment with senolytic drugs results in the elimination of senescent cells, thus blocking tissue degeneration and late life complications. In turn, elimination of senescent cells leads to the proliferation of stem cells, allowing tissue regeneration.

Using a transcriptomics approach, some proteins and pathways that aid in senescent cell survival and apoptosis resistance, such as ephrins (EFNB1 and EFNB3), phosphatidylinositol-4,5-bisphosphate 3-kinase delta catalytic subunit (PI3KCD), p21, B-cell lymphoma-extra-large (BCL-xL), and plasminogen-activated inhibitor-2 (PAI-2), were identified [38]. Drugs that target these pathways were tested as candidate senolytics (Table 2).[10]

Table 2. Potential senolytic drugs [10]

Agent	Pharmacological class	Proposed molecular target	Findings related to pulmonary diseases
Dasatinib	Tyrosine kinase inhibitors	Pan-receptor tyrosine kinase inhibitor with markedly high affinity for BCR/ABL kinase and ability to inhibit a large number of kinases, including the Src family kinases, and also block EFNB-dependent receptor signaling	In patients with systemic sclerosis–associated interstitial lung disease, dasatinib was associated with acceptable safety profile but no significant clinical efficacy. It induces pulmonary endothelial damage, with an increased susceptibility to pulmonary hypertension in rodent experimental models and in patients with chronic myeloid leukemia
Quercetin	Flavonoids	It is a strong antioxidant, induces cell apoptosis in various cancer cells by inhibiting specific antiapoptotic genes such as PI3K and other kinases, and partially inhibits serpins	It diminished the proinflammatory phenotype of bleomycin-induced senescence in fibroblasts in vitro. It reduced the IL-13, PDGF-β, and TNF-α and increased the level of the antifibrotic factor interferon-γ. Reduction of bleomycin-induced collagen

			deposition and enzyme activity of MMP-7 in lung tissues; improvement of antioxidant–oxidant imbalance.
Dasatinib + quercetin			They deplete senescent cells by inducing apoptosis and reduced SASP factors in mouse primary AECIIs, and improve lung function and indicators of fibrotic disease following bleomycin injury. This combination killed irradiation-induced senescent primary human fibroblasts more efficiently than navitoclax in vitro
Fisetin	Flavonoids	It is an antioxidant and targets PI3K/AKT/metabolic pathway	Anti-inflammatory and antioxidant effects. It normalized the bleomycin-induced increase in inflammatory cell count and inhibition of cellular recruitment to the spleen
Navitoclax (ABT-263)	BCL-2 family inhibitors	It targets both the antiapoptotic proteins BCL-xL and BCL-2	It reduced senescent cells and reversed the disease in irradiated mice after persistent pulmonary fibrosis had developed
A1331852 and A1155463	BCL-xL inhibitors	Ligands of BCL-xL, binding to the target potently and selectively, highly selective against closely related proteins of BCL-2, BCL-W, and MCL-1	
17-AAG, 17-DMAG, and geldanamycin	HSP-90 inhibitors	They block HSP-90, which is important in conferring cell survival	
FOXO4 D-retro inverso isoform	Retro inverso peptides	Directed at perturbing FOXO4−p53 interaction. It inhibits the PI3K/AKT/p53/p21/serpine SCAP and blocks an association with p53	

Metformin	Biguanides	It prevents the translocation of NF-κB to the nucleus and inhibited the phosphorylation of IκB and IKKα/β. It is also able to increase in DICER1	Reduced risk of COPD
Rapamycin	Immunosuppressors	It inhibits mTOR activity and can raise levels of Nrf2	It can decrease the increased propensity of lung cells to senescence

AECIIs, alveolar epithelial type II cells; BCL-2, B-cell lymphoma 2; BCL-xL, B-cell lymphoma-extra-large; FOXO4, forkhead box protein O4; HSP-90, heat shock protein 90; IκB; inhibitor of kB; IKK, IκB kinase; IL, interleukin; MMP-7, matrix metalloproteinase-7; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; Nrf2, nuclear factor E2-related factor 2; PDGF, platelet-derived growth factor; PI3K, phosphoinositide-3-kinase; SASP, senescenceassociated secretory phenotype; SCAP, senescent cell antiapoptotic pathway; TNF-α, tumor necrosis factor-α.

Dasatinib, quercetin, and **navitoclax** (ABT-263) were developed to treat cancer cells.[31] **Dasatinib** is a tyrosine kinase inhibitor with markedly high affinity for BCR/ABL kinase and ability to inhibit a large number of kinases, including the Src family kinases, and also to block EFNB-dependent receptor signaling; quercetin, a flavonoid, is a strong antioxidant, induces cell apoptosis in various cancer cells by inhibiting specific antiapoptotic genes such as PI3K and other kinases, and partially inhibits serpins; navitoclax is a B-cell lymphoma 2 (BCL-2) inhibitor that has been tested in lymphoid malignancies. However, it has become evident that these anticancer drugs could be used as drugs to remove senescent cells due to their common site of action between cancer and senescent cells. **Dasatinib** can inhibit the proliferation and kinase activity in senescent cells and to increase cell death in senescent cells compared to nonsenescent human preadipocytes by inhibiting pathways that are closely linked to cellular senescence. **Quercetin** preferentially induces cell death in senescent relative to nonsenescent human umbilical vein cells (HUVECs). There is some appearance of cell type selectivity for each compound, but their effects are enhanced and broadened when given in combination.[32]

Combination of **dasatinib** and **quercetin** reduced senescent cells in fat and liver tissues of old mice, as well as in muscle and fat tissues of irradiated mice. Moreover, this combined treatment alleviated several age-related pathologies, such as impaired cardiovascular function and extended health span of the Ercc1−/Δ progeroid mouse model of accelerated aging, supporting the therapeutic potential of eliminating senescent cells at old age.[29]

Navitoclax, which targets both the antiapoptotic proteins BCL-xL and BCL-2, selectively kills senescent cells in culture in a cell type- and species-independent manner by inducing apoptosis. However, usage of navitoclax as a prophylactic senolytic drug is unlikely because of its severe thrombocytopenic and neutropenic effects.[33]

Similarly, **fisetin**, which is a member of the flavonoid family, and the selective BCL-xL inhibitors, A1331852 and A1155463, are senolytic in vitro, inducing apoptosis in senescent but not nonsenescent HUVECs. Also, piperlongumine, a natural product isolated from a variety of species in the genus Piper, can produce senolytic activity in certain cell types in culture, although the precise mechanism of action by which it induces senescent cells apoptosis remains unclear.[34]

Rapamycin is one of the only medications that can extend life in a variety of species by blocking mTOR activity. Mechanistically, it can increase levels of the prolongevity signalling pathway nuclear factor E2-

related factor 2 (Nrf2), which are typically decreased in senescent tissue, hence lowering cell senescence by activating autophagy. In animal models, rapamycin exhibits great promise as a medication for the management of age-related illnesses. Its long-term usefulness in humans is, however, limited by the notable adverse consequences. It's conceivable that rapalogs and mTOR kinase inhibitors will experience comparable issues. Additionally, dual mTOR kinase inhibitors, or mTORins, are promising antiaging medications. However, many questions remain, including appropriate dosage, toxicity, and side effects.[35]
The oral hypoglycemic medication **metformin** influences a number of aging-related mechanisms, including autophagy, protein synthesis, inflammation, and cell survival. Its antisenescence and anti-inflammatory properties have been explained by a number of mechanisms, including direct or indirect effects on the mTOR activity and the NF-κB pathway. The phosphorylation of IκB and IκB kinase (IKK)α/β, which are necessary for the activation of the NF-κB pathway, is blocked by metformin, as is the translocation of NF-κB to the nucleus. Moreover, there is proof that metformin can reduce cellular senescence in various senescence models in a DICER1-dependent way and raise DICER1, a crucial enzyme that processes micro-RNAs.[36]

SENOLYTICS IN VIRAL INFECTION

The recent COVID-19 pandemic underscored the heightened risk faced by the elderly and individuals with pre-existing conditions, such as obesity, type 2 diabetes, and chronic kidney disease, in experiencing adverse outcomes following acute pathogen exposure. This vulnerability was likely driven by cytokine storms. A plausible explanation was that a higher burden of senescent cells (Snc) in these populations contributed to their susceptibility to pathogen-driven inflammation. Pathogen-associated molecular pattern molecules (PAMPs), which are microbe-derived molecules that activate innate immunity via pattern recognition receptors, may have amplified the senescence-associated secretory phenotype (SASP) of pre-existing Sncs, leading to a highly inflammatory, profibrotic secretome. If this hypothesis held true, senolytics could have been employed to prevent or treat individuals with a high burden of Sncs, thereby reducing morbidity and mortality following infections such as SARS-CoV-2 (COVID-19) or influenza.[1]
The mortality rate from COVID-19 was notably greater in older persons, raising concerns about the potential link between COVID-19 infection and chronological ageing. Senescence was linked to two host receptors for COVID-19: CD26 and ACE-2 (angiotensin-converting enzyme 2). **Azithromycin** and **quercetin**, two suggested COVID-19 therapies, also showed signs of senolytic action. Moreover, chemicals related to chloroquine prevented the production of beta-galactosidase, a hallmark of senescence. Additional anti-aging medications, such as **Doxycycline** and **Rapamycin**, prevented viral replication and suppressed protein synthesis.
Thus, it seemed reasonable to hypothesise that senolytics and other anti-aging medications were important in both treating and preventing COVID-19. New clinical trials were necessary to test this theory, particularly since a number of senolytic and anti-aging treatments already had FDA approval and good safety records, making them perfect candidates for medication repurposing. We ought to have thought of using this family of antibiotics, which functionally impeded cellular protein synthesis, for the treatment and prevention of COVID-19, as conventional antibiotics like **Azithromycin** and **Doxycycline** inhibited viral replication and the creation of IL-6.

PHYTOCHEMICALS WITH ANTI-AGING PROPERTIES AND THEIR ASSOCIATED MECHANISMS FOR EXTENDING LIFESPAN:

Biological sciences regarding ageing are among the most well-known yet least understood. From a physiological perspective, it is defined as a progressive, generalised, systematic dysfunction of nearly every organ, which increases susceptibility to environmental stressors and raises the risk of illness and death. In fact, a variety of degenerative diseases, including as cancer, Alzheimer's disease, Type 2 diabetes, and cardiovascular disease, are far more common in older adults. These chronic illnesses account for almost 70% of fatalities in the United States. Thus, one of the most important ways to support good ageing is to stop or slow the pathophysiology of these chronic diseases. It's interesting to note that oxidative stress, increasing levels of chronic, low-grade inflammation, accumulating mutations in DNA, and increased damage to the DNA are all strongly correlated with ageing and chronic diseases.[38] Targeting nutrient-sensing and energy metabolism pathways may be a useful strategy to postpone the ageing process and age-related diseases, as it is well known that calorie restriction increases longevity in a variety of animals and delays age-associated organ abnormalities. Recent research has indicated that certain phytochemicals may be able to lower the risk of chronic illnesses, even though they are not thought to be necessary nutrients. The majority of phytochemicals are secondary plant metab olites that can be found in a wide range of foods and beverages, such as juice, tea, cereals, nuts, fruit, chocolate, coffee and wine. More than 1 g of phytochemicals per day is commonly ingested with the diet. There are seven main categories of phytochemicals, including phenolic compounds, terpenes, betalians, organosulfides, indoles/glucosinolates/sulfur compounds, protein inhibitors and other organic acids (Table 3).[41] Phenolic compounds, also known as polyphenols, are the largest, most studied group. For example, tea flavan-3-ols (epigallocatechin gallate, EGCG), berry anthocyanins, soy isoflavones, and grape stibenoids resveratrol are in this category. Provitamin A carotenes from carrots and pumpkins, limonene from oils of citrus and cherries, saponins from legumes belong to terpenes.[39] Although tocopherol (vitamin E) and omega-3 fatty acids are included in terpenes as phytochemicals and may have antiaging potential.[38] Many phytochemicals have been well studied for their abilities to prevent or treat chronic diseases, and there are several reviews in terms of the actions of phytochemicals in prevention and treatment of cancer, cardiovascular disease, obesity, diabetes, as well as neurological dysfunctions.[42][43][44] Recently, emerging evidence shows that some food-derived bioactive compounds have antiaging capabilities, although studies in this field are still relatively limited. This review summarizes several major potential anti-aging phytochemicals or “phytonutrients” that have been studied in cells, animals, and humans, and further highlights the possible mechanisms by which these molecules delay the aging process.[37]

Table 3: Classification of phytochemicals and their food sources [37]

Category			Chemical	Food/Plant resources
Phenolic compounds	Natural monophenols		Rosemarinol	Rosemary
	Flavonoids (polyphenols)	Flavonols	Quercetin	Onions, tea, wine, apples
			Kaempferol	Tea, strawberries, gooseberries
			Fisetin	Tea, grape, onions
			Myricetin	Grapes, red wine, berries

		Flavanones	Naringenin	Citrus fruits
		Flavones	Apigenin	Chamomile, celery, parsley
			Luteolin	Beets, artichokes, celery
		Flavan-3-ols	Catechin	white tea, green tea, black tea
			(−)-Epicatechin	Tea, cocoa, grape
			EGCG	green tea
			Theaflavin	Black tea
		Anthocyanins/	Pelargonidin	Bilberry, raspberry, strawberry
		Anthocyanidins	Delphinidin	Bilberry, blueberry, eggplant
		Isoflavones	Genistein	Soy, red clover, peanuts
		Chalconoids	Butein	Rhus verniciflua, dalbergia odorifera
			Phlorizin	Pear, apple, cherry
	Phenolic acids		Ellagic acid	Walnuts, strawberries, cranberries
			Curcumin	Turmeric, mustard
	Hydroxycinnamic acids		Caffeic acid	Burdock, hawthorn, artichoke
	Lignans		Matairesinol	Flax seed, sesame seed, rye bran
	Tyrosol esters		Tyrosol	olive oil
	Stilbenoids		Resveratrol	Grape, wine, nuts
	Alkylresorcinols			Wheat, rye and barley
Terpenes	Carotenoids	Carotenes	Carotene	Carrots, pumpkins, maize,
		Xanthophylls	Lutein	Spinach, turnip greens, lettuce

	Monoterpene	Limonene		Oils of citrus, cherries, spearmint
	Saponins			Soybeans, beans, other legumes
	Lipids	Phytosterols	Sitosterol	Avocados, almonds, wheat germ
	Triterpenoid	Glaucarubinone		Simaroubaceae plants
Betalains	Betacyanins	Betanin		Beets, chard
	Betaxanthins	Indicaxanthin		Beets, sicilian prickly pear
Organosulfides	Polysulfides	Allyl methyl trisulfide		Garlic, onions, leeks
Indoles, glucosinolates/ sulfur compunds	Indole-3-carbinol			Cabbage, kale, brussels sprouts
	Sulforaphane			Broccoli, cauliflower, brussels sprouts
	Allicin			Garlic
Protein inhibitors	Protease inhibitors			Soy, legumes
Other organic acids	Oxalic acid			Orange, spinach, rhubarb
	Anacardic acid			Cashews, mangoes

ANTIAGING PHYTOCHEMICALS

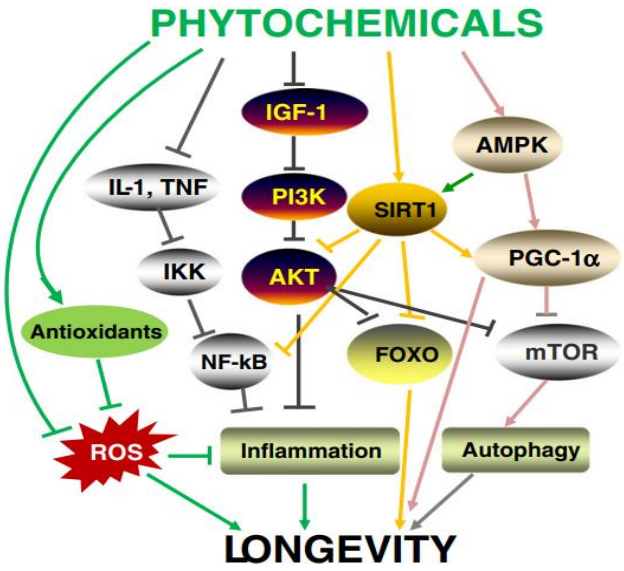

Fig 1. Hypothetical cellular and molecular mechanisms of the antiaging effects of phytochemicals. Phytochemicals extend lifespan through reducing oxidative stress, suppressing low-grade chronic inflammation, and inducing autophagy. As shown, there are cross talk and interaction at both cellular and molecular levels between these events.[37]

Resveratrol

A polyphenolic tiny molecule called resveratrol (3,5,4′-trihydroxystilbene) can be found in a wide variety of plant-based foods, including chocolate, hellebore, peanuts, red wine, and grapes.[45] Although it is well known that a high intake of saturated fat is linked to a high incidence of heart disease, an intriguing epidemiological finding from about 20 years ago suggested that French people who regularly drink red wine and eat a diet high in saturated fat had a lower incidence of coronary heart disease and lived longer. There has been much interest in the scientific world to investigate the possible health benefits of red wine since it was discovered to contain a considerable amount of resveratrol. This has led to conjecture that consuming red wine may have health benefits due to resveratrol. One important stage in the development of coronary heart disease is the oxidation of low-density lipoproteins, which is inhibited by resveratrol in wine at concentrations of up to 30 mg/L. Furthermore, a large amount of research showed that resveratrol supplementation in the diet has positive effects on ageing and a number of other chronic human disorders. Resveratrol has been shown to offer protection against Alzheimer's disease, diabetes, and cancer.[46] Furthermore, resveratrol was shown to increase the lifespan of yeast by 70%, a well-known model in the study of ageing. Additional research revealed that resveratrol supplementation can enhance health and lengthen the life span of fish, Drosophila melanogaster (Drosophila), and Caenorhabditis elegans (C. elegans) in some ways, similar to how calorie restriction works.

Together with these results, a number of mouse model studies also showed that, when treatment began at around one year of age, dietary provision of a moderate amount of resveratrol (0.01% or 0.04%) improved health and increased lifespan of obese male mice (C57B6) induced by high-fat diet by 26 and 25%, respectively. Resveratrol-treated obese mice consistently showed a number of physiological changes linked to a longer and healthier life. Interestingly, it was also discovered that resveratrol treatment had a variety of other positive effects on mice that mirrored some of the physiological and transcriptional changes brought on by calorie restriction, resulting in an overall healthier life for these mice, even though the longevity of standard diet-fed mice was not increased. In fact, in aged rats on a high-fat diet, resveratrol treatment reverses the effects of insulin resistance, oxidative stress, inflammation, vascular dysfunction, osteoporosis, cataracts, and the loss of motor coordination. Resveratrol specifically lowers the frequency of fatalities brought on by severe lung congestion and edoema together with fatty changes in the liver, which are partly related to continuous feeding of a high-fat diet. As cardiovascular disease is a major cause of age-related morbidity and mortality in humans, resveratrol may have a promising antiaging effect. Although there is still no conclusive evidence that resveratrol intake can extend lifespan in humans, results from several relatively short-term studies suggest that resveratrol improved insulin resistance, blood flow, and various cardiovascular events as well as decreased oxidative stress and inflammation. The potential benefits of pure resveratrol or products containing resveratrol on a range of age-related health conditions, including obesity, insulin resistance, impaired glucose tolerance, dyslipidemia, inflammation, cognitive function, and Type 2 diabetes, are currently being evaluated in a number of ongoing clinical trials.[47]

Epicatechin

Flavanols called epicatechin can be found in a variety of foods, including berries, apples, chocolate, grapes, pears, and tea. Of these, cocoa beans have the highest concentration of epicatechin (43,270 mg/kg

fresh weight) as compared to green tea (8,000 mg/kg). According to epidemiological research, people who live on San Blas Island, where cocoa is consumed in significant quantities, had lower rates of diabetes, stroke, and ischemic heart disease than people who live in mainland Panama. They also appear to have longer lifespans. When they relocate to Panama City and cut back on their cocoa intake, these advantages vanish. Consuming chocolate on a diet has been associated with a 4-year improvement in life expectancy. Products containing cocoa improve aging-related blood vessel function, insulin sensitivity, blood pressure, and inflammation. Due to increased levels of plasma nitric oxide, flavanol-rich cocoa improves blood vessel dilatation in individuals with type 2 diabetes and promotes flow-mediated vasodilation. Research on epicatechin demonstrates that it increases lifespan in Drosophila, C. elegans, old rats, and diabetic mice. This effect may be attributed to lowered LDL cholesterol, enhanced hepatic antioxidants, decreased IGF-1, and enhanced AMPKα activation. These results imply that epicatechin may be a new chemical that extends human health.[48]

Quercetin

A common flavonoid found in a wide variety of fruits and vegetables, such as grapes, blueberries, cherries, onions, apples, and broccoli, is quercetin (3,3,4,5,7-pentahydroxyflavone). It has been documented that a 200 mM quercetin treatment increased C. elegans' lifespan by 20%. Curiously, the lifespan-extension effect of quercetin in C. elegans was eliminated by recessive mutation of the genes age-1 or daf-2 (encoding for the IGF-1 receptor in C. elegans), two important players in the metabolic pathway to regulate the rate of ageing. This suggests that quercetin may extend lifespan in the worms by either directly or indirectly inhibiting the age-1 and daf-2-mediated pathways. According to a recent study, by activating the proteasome, quercetin and its derivative quercetin caprylate can regenerate senescent fibroblasts and lengthen their longevity. It has been observed that quercetin is the most effective flavonoid scavenger of reactive oxygen species (ROS), with a potency nearly six times greater than that of vitamin C or trolox, the reference antioxidant. Furthermore, quercetin has potent anti-inflammatory properties by preventing immune cells from producing interleulin-1α and tumour necrosis factor-α in response to lipopolysaccharides.[49] Given that persistent oxidative stress and inflammation are thought to be major contributors to the ageing process, these antioxidant and anti-inflammatory qualities may help explain why quercetin and its derivatives have an antiaging impact.

Curcumin

A significant curcuminoid found in 31 species of curcuma plants, including Curcuma longa, whose rhizome yields the spice turmeric, is curcumin (diferuloylmethane). Turmeric's yellow colour is mostly caused by curcumin, a lipophilic phenolic molecule that can make up as much as 5.4% of raw turmeric. Curcumin I (94%) consists of curcumin II (6%), and curcumin III (0.3%) together make up curcumin. For many decades, curcumin has been used in traditional Chinese and Indian medicine to treat a wide range of conditions, such as ulcers, jaundice, acne, sprains, wounds, upset stomach, flatulence, dysentery, and infections of the skin and eyes. Consuming curcumin through diet is thought to be safe, and its possible health benefits have been thoroughly researched. A growing body of research demonstrates that curcumin supplements lengthen the lives of Drosophila and C. elegans, and that dietary consumption of tetrahydrocurcumin, a metabolite of curcumin, at a rate of 0.2% dramatically enhanced the survival rate of mice. Furthermore, piperine, an alkaloid found in black pepper, and curcumin together reduced the senescence that rats experienced from D-galactose.[50] Curcumin also has antioxidant and anti-inflammatory qualities, which may further add to its possible antiaging benefits.

Green tea extract and EGCG

After water, tea is the most popular beverage in the world. Green tea extract is gaining popularity as a nutritional supplement in the US due to potential benefits for conditions like obesity, diabetes, cancer, heart disease, and neurological diseases. It was not until recently that green tea extract and its main bioactive ingredient, epigallocatechin gallate, were shown to have antiaging properties. However, the majority of these research were conducted on rodents or other smaller model species. When C. elegans is kept under normal or oxidative stress conditions, EGCG consistently lengthens its longevity.[51] The average lifespan of male C57BL/6 mice fed a normal diet is increased from 801 days to 852 days by green tea extract (80 mg/L) containing 18.0% EGCG, 11.6% (−)-gallocatechin 3-O-gallate, 4.6% (−)-epicatechin 3-O-gallate, 15.0% (−)-epigallocatechin, 14.8% (+)-gallocatechin, 7.0% (−)-epicatechin, and 3.5% (+)-catechin.[54] In elderly male C57BL/6 mice, diet supplemented with a combination of 2% blueberry extract, 0.0115% EGCG, and 0.3% pomegranate powder enhanced the effects of calorie restriction on longevity. Nevertheless, a recent study by the National Institute on Ageing Interventions Testing Programme found that giving 2% green tea extract to genetically heterogeneous male and female mice for the rest of their lives, starting at 4 months of age, reduced the risk of midlife deaths in female mice but did not significantly increase their lifespan.[47] Consequently, the genetic background of the mouse and/or the existence of particular environmental factors, such as dietary stress, may affect the antiaging efficacy of green tea extract and EGCG. Furthermore, the duration, dosage, and age of the animal at which the intervention starts might all have an impact on the result. Research evaluating the anti-aging effects of green tea extracts on humans are scarce; nonetheless, an intriguing cohort research reveals that regular use of green tea dramatically lowers the death rate among Japanese women. This outcome partially agrees with the conclusions of the rodent study mentioned above. Nevertheless, additional research is required to ascertain whether green tea extract affects longevity differently in men and women.[52]

Urolithin A

It was discovered that urolithin A activates mitophagy, preventing the build-up of unhealthy mitochondria. Studies revealed that urolithin A feeding from eggs until death increased the lifespan of C. elegans by 45.4%. Furthermore, urolithin A can stop cells from maliciously accumulating damaged mitochondria. Experiments conducted on rats revealed that an eight-month urolithin A treatment, starting at age sixteen months, significantly increased muscular performance in mice fed a high-fat diet when compared to the control group. The 6-week urolithin A treatment of 22.5-month-old mice on a regular chow diet produced similar beneficial outcomes, with an average improvement in running endurance of 42%. Young rats also showed the beneficial effects of urolithin A, with improvements in their exercise capacity.[53]

Urolithin A's first human clinical trial (NCT02655393) was recently carried out on healthy, sedentary elderly human individuals. The outcomes demonstrated a molecular signature response and a safety profile that suggested enhanced mitochondrial health.[55] This lends credence to a potentially effective strategy of using dietary urolithin A consumption as an intervention to enhance muscle and mitochondrial function and support human health as we age. It has been demonstrated that urolithin A controls several metabolic pathways. In animal experiments, Urolithin A has been shown to have anti-inflammatory and anti-obesity properties in addition to stimulating mitophagy. In rodents and human cell culture, urolithin A and its synthetic analogue UAS03 can improve the integrity of the intestinal barrier and decrease inflammation by initiating pathways that are dependent on the aryl hydrocarbon receptor (AhR) and nuclear factor erythroid 2–related factor 2 (Nrf2). By promoting thermogenesis in brown adipose tissue and causing browning of white adipose tissue, urolithin A can also raise energy expenditure and prevent diet-induced

obesity in mice.[56] A novel natural food metabolite called urolithin A has been shown in human clinical trials to be effective in promoting mitophagy and enhancing mitochondrial functioning. Treatment for diseases and problems associated with ageing may depend on mitophagy. It may be possible to promote mitophagy by targeting deubiquitylating enzymes.[57]

Capsaicin

Chilli peppers contain capsaicin, which is an agonist of TRPV1 (Transient receptor potential channels are cation channels that sense a wide spectrum of ambient temperatures) and may extend life. Numerous human studies on diets high in capsaicin attest to this. According to a recent Italian study,[58] 22,811 residents who took part in the Moli-Sani Study between 2005 and 2010 were the subject of the study. For a median follow-up of 8.2 years, the researchers compared the dietary habits of the participants and performed a follow-up survey regarding their health problems. Researchers discovered that those who consumed chilli peppers on a regular basis (four times a week) showed a 23% decrease in the risk of death from all causes and a more than 50% decrease in the chance of death from cerebrovascular accidents. It is noteworthy to note that eating a lot of chilli peppers lowers the chance of death even for those who do not consume a healthy Mediterranean diet.[58] This implies that chilli peppers themselves are good for human health. Scientists examined the health effects of eating spicy food among Chinese residents for a median follow-up of 7.2 years among 512,891 participants between the ages of 30 and 79, prior to the study on chilli pepper intake and mortality in Italians. According to the findings, persons who ate spicy food six or seven days a week had a 14% lower relative risk of dying overall than those who ate it fewer than once a week. Additionally, there are strong negative correlations between eating spicy food and death from respiratory illnesses, ischemic heart disease, and cancer.[59] In addition to surveys carried out in Europe and Asia, demographic studies conducted in North America corroborated the beneficial effects of eating spicy cuisine on ageing. In the US study, total mortality was 12% lower in patients who ate spicy red chilli peppers throughout the course of a median of 18.9 years, compared to 16,179 other participants.[59]

Other phytochemicals/plant-extracts

It has been shown that aged garlic extract, which contains diallosulfides, s-allycisteine, s-allymercaptocysteine, and allicin, lengthens mice's lives and improves their cognitive abilities.[60] Two phytochemicals from fruits and the Chinese lacquer tree, butein and fisetin (10 mM), increased the longevity of Saccharomyces cerevisiae by 33% and 5%, respectively. It has been discovered that phenolidzin, a dihydrochalcone found in high concentration in apples, lengthens the life of yeast via controlling SOD and Sir2, a protein deacetylase that is dependent on nicotinamide adenine dinucleotide (NAD)+. It has also been discovered that kaempferol, a flavonoid found in ginkgo biloba, grapefruit, tea, broccoli, and berries, increases the lifetime of C. elegans by enhancing its antioxidant capacity and daf-16 translocation. Glaucarubinone, a cytotoxic and antimalarial quassinoid derived from several simaroubaceae plant species, increases mitochondrial metabolism, and lengthens C. elegans' life span.

Given that the effective levels of glaucarubinone are just 10–100 nM, it looks to be a more potent antiaging agent than many other natural chemicals addressed in the research. Additionally, it was discovered that blueberry extracts lengthened the life of C. elegans. This finding may be primarily attributed to pro-anthocyanidins, a class of flavanols or polyphenols, as isolated pro-anthocyanidins from blueberries demonstrated an antiaging effect comparable to that of whole blueberry extracts.[60] To our knowledge, no published research has examined the impact of these phytochemicals on the ageing process in vertebrate animals.

Herbal remedies have shown promise in China during the COVID-19 pandemic in symptom reduction. Additionally, there is evidence that functional food ingredients, when taken as a nutritional supplement, can either help people recover more quickly from COVID-19 infection or avoid it altogether by enhancing immune function.[61] Therefore, natural phytochemicals may be a priceless resource for treating illnesses and delaying the ageing process in humans. For instance, there is a lot of quercetin in the black chokeberry extract, which has been shown to have health benefits including extending life, avoiding neurological disorders, enhancing glucose and lipid metabolism, and anti-proliferation.[62]

Everyday consumable fruits including pomegranates, cherries, apples, and grapes also include urolithin A, fisetin, and other compounds covered in this article. To achieve healthy ageing and to enable individualised dietary approaches that strike a balance between health and personal preferences, more research is needed to fully understand the effects and mechanisms of dietary ingredients on longevity regulation.

ANTI-AGING STRATEGIES FOR COGNITIVE DISEASES

Alzheimer's disease (AD) is a neurodegenerative disease which is the main cause of dementia worldwide, and it is currently incurable. It is characterized by a loss of memory and progressive cognitive, functional, and behavioral decline that interferes with daily life.[63] It is now well recognized that the pathogenesis begins up to one or two decades before the onset of the clinical symptoms.[64] Therefore, understanding the mechanisms that lead to the progression of the disease is essential to establish an early diagnosis and slow or prevent its progression.

The two hallmarks of AD are the accumulation of extracellular senile plaques formed by amyloid beta (Aβ) peptides, and the accumulation of hyperphosphorylated tau aggregates that form neurofibrillary tangles (NFTs) inside neurons. In addition to plaques and NFTs, oxidative damage to proteins, nucleic acids, and lipids plays a key role in the pathophysiology of the disease, as in most age-related ailments.[65] It has been reported that Aβ promotes the generation of reactive oxygen species (ROS), either directly or indirectly, by triggering N-methyl-D-aspartate receptor-dependent Ca2+ influxes and leading to mitochondrial dysfunction. However, it has been postulated that Aβ accumulation may be a consequence of oxidative stress and that Aβ and tau act as antioxidants in AD (reviewed by Sutherland et al.). Although this issue is still unclear, a wide range of studies have shown that the imbalance between the production of ROS, on the one hand, and antioxidant defenses, on the other, contribute considerably to the pathogenesis and progression of AD.[65] In fact, considerable attention in AD research has been focused on identifying compounds capable of scavenging excess ROS.

Resveratrol (RV; trans-3,40 ,5-trihydroxystilbene) and **selenium** (Se), which are both nutraceuticals with antioxidant properties that can permeate the brain blood barrier, seem to have therapeutic potential as neuroprotective agents.[66] RV is a polyphenol that is mainly found in some fruits such as blueberries, blackberries and grapes, and also in peanuts. It has been shown that RV mimics the anti-aging and neuroprotective effects of caloric restriction through sirtuin 1 (SIRT1) mechanisms.[67] RV indirectly activates SIRT1 through cAMP signaling that leads to activation of the 50 AMP-activated protein kinase (AMPK)/SIRT1 pathway. Furthermore, both in vitro and in vivo experimental AD studies have suggested that RV activates the SIRT1 pathway as its main neuroprotective mechanism. However, RV may partially act through other mechanisms, as demonstrated by in vitro treatments in the presence of the SIRT1 inhibitor sirtinol, where RV neuroprotection was only partially abolished. In this regard, RV has potent antioxidant properties through direct scavenging of ROS. Some clinical trials have shown that resveratrol

is safe, well-tolerated, and is capable of decreasing neuroinflammation and modifying some AD biomarkers, such as cerebrospinal fluid Aβ40 and Aβ42.[68]

Selenium is an essential micronutrient for brain function that plays a critical role in multiple metabolic pathways, including those involved in antioxidant defense in organisms. Se is a component of antioxidant enzymes, such as glutathione peroxidase, and there are a number of other selenoenzymes and selenoproteins. There are two different commonly occurring forms of Se in nature, selenite (Se (IV)) and selenate (Se (VI)), and both have been studied in the context of the prevention of AD onset and progression. Studies have shown that diets supplemented with these components can play a neuroprotective role in AD experimental models.[69] For example, Se (IV) can reduce the amount of Aβ plaques and Se (VI) may reduce hyperphosphorylation of tau. Studies in humans have found a significant decrease of Se in AD brains or blood cells, compared to controls.[69] Therefore, both RV and Se diet supplementation are promising strategies to combat aging and AD.

Metformin

As the first-line treatment for people with type 2 diabetes, metformin is a cheap, safe, and often given glucose-lowering medication that has been shown to successfully minimise the risk of cardiovascular disease and death.[70] When compared to other antidiabetic medications, older adults who take metformin have a lower risk of hypoglycemia and non-fatal cardiovascular events.[71] It has demonstrated many beneficial effects in patients with a variety of conditions, including impaired glucose tolerance, obesity, metabolic syndrome, polycystic ovary syndrome (PCOS), and non-alcoholic fatty liver disease, in addition to its direct hypoglycemic effects and prevention of target-organ damage in T2D patients.

Metformin and Cognitive Function

There is currently conflicting information regarding how metformin affects older people's cognitive deterioration. While some research involving diabetic patients highlighted the preventive effect of metformin against cognitive decline, other investigations asserted that metformin exposure is linked to neurodegeneration, Parkinson's disease, and Alzheimer's disease. The frequent comorbidity of T2D patients, the need to administer many medications, and the practical difficulties of evaluating the exclusive benefit of metformin alone all contribute to the contradictory outcomes of these research. Cognitive decline may sometimes result from other coexisting illnesses and not always from any kind of pharmaceutical intervention. According to a cross-sectional study by D. Hervás and colleagues, patients with Huntington's disease who take metformin have improved cognitive function.[72] Further large-scale prospective controlled trials that concentrate on the cognitive function of patients assigned to metformin are needed. Several intriguing studies have recently been planned and conducted that assess the unique benefits of metformin as an antiaging medication, with a focus on age-related disorders in people. The goal of the Metformin in Longevity Study (MILES) is to ascertain whether elderly patients with reduced glucose tolerance may benefit from taking 1700 mg of metformin daily to potentially restore gene expression. The first randomised controlled clinical experiment to assess metformin as an anti-aging medication is called the Targeting Ageing with Metformin (TAME) trial. The initial trial result is the duration until any of the multimorbidity composite associated with ageing (heart disease, stroke, congestive heart failure, peripheral arterial disease, cancer, type 2 diabetes, cognitive decline, and death).[73]

Aspirin

Acetylsalicylic acid, or aspirin, is one of the most often prescribed drugs in the world. Originally created as an analgesic and antipyretic, this medication made history by being mostly utilised for primary and

secondary cardiovascular prevention today. Many of its complementing effects on age-related disorders, however, are still unknown.[74] Aspirin's low cost, ease of use, and well-researched multidimensional qualities regarding cardiovascular disease (CVD) and cancer make it a potentially highly suitable agent to be designated as a promising antiaging medicine.

Aspirin and Cognitive Function

The possible benefits of antiplatelet actions in neuroprotection may include a reduction in impairments brought on by minor neurovascular lesions. The evidence, however, is not very encouraging when it comes to aspirin users potentially buffering cognitive decline. Patients from the Women's Health Initiative Memory research of Magnetic Resonance Imaging research had the specific impact of ASA on brain white matter lesions (WML) assessed. WML volumes did not significantly change between aspirin users and non-users.[75] Additionally, studies on Alzheimer's patients have shown that using ASA does not offer any significant therapeutic advantage. Moreover, individuals using ASA run a high risk of experiencing greater cognitive loss because of the increased risk of intracerebral haemorrhage. Veronese et al.'s recent meta-analysis[76] of data from 36,196 individuals did not support aspirin's preventive effect against cognitive deterioration as people age. The use of low-dose aspirin was not linked to a substantial improvement in overall cognition, the start of dementia, or cognitive impairment, according to pooled data from RCTs and observational studies. By the end of 2018, the ASPREE study (ASPirin in Reducing Events in the Elderly) will have completed its assessment of the function of aspirin in maintaining a life free from dementia and disability in a healthy elderly population. This study's use of advanced neurovisualization tools may help us understand how to prevent microvascular dementia with ASA. The trial also seeks to determine whether possible advantages outweigh the risks in this specific population.[77]

CONCLUSION

Finally, exciting new approaches to preventing age-related illnesses and prolonging life spans are being presented by the developing fields of senolytics and anti-senescence interventions. In preclinical trials, these medicines have demonstrated potential to ease frailty, and targeting age-related ailments, a variety of chronic illnesses, improve physical function, and promote resilience by targeting senescent cells and the underlying mechanisms of ageing additional investigation is necessary to comprehensively grasp their effectiveness and safety in human subjects. Approaches for evaluating these interventions through clinical trials are changing, with an emphasis on objectives including improved physiological resilience, alleviation of frailty, and decrease of multimorbidity. Furthermore, the identification of senolytic drugs and their mechanisms of action may be useful in the development of targeted therapies that preserve healthy tissues while selectively eradicating senescent cells. The study suggests that abnormal aging contributes to the development of IPF and COPD, indicating a need for novel approaches to slow lung aging in these disorders. Senolytic drugs, which selectively eliminate senescent cells, show promise in preclinical studies for treating IPF, warranting proof-of-principle clinical trials. However, the evidence is not robust, and there are concerns about potential harm in IPF patients. Despite extensive research, effective pharmacological approaches for preventing cognitive diseases remain elusive. Aging, a major risk factor for cognitive disorders, is now seen as modifiable based on recent aging biology research. Numerous preclinical studies have shown that aging can be influenced by pharmacological interventions, though the translation of these findings to clinical applications is challenging. Few studies focus on brain aging as a primary cause of cognitive disorders or apply antiaging interventions to delay cognitive decline. A thorough evaluation of novel antiaging compounds for their impact on brain aging Alzheimer’s disease

and dementia is warranted, and closer collaboration between aging biology and clinical neurobiology researchers could greatly benefit geriatrics and gerontology. The study also suggests that phytochemicals such as resveratrol, green tea extract, EGCG, epicatechin, quercetin, and curcumin have potential antiaging effects through mechanisms like reducing oxidative stress, suppressing chronic inflammation, inducing autophagy, and regulating mitochondrial function and energy homeostasis ,these mechanisms are like those observed with calorie restriction, indicating that dietary intake of these compounds might promote healthy aging. However, phytochemicals did not extend lifespan in all models, suggesting they may primarily correct metabolic alterations caused by excessive calorie intake, thus delaying age-related diseases and promoting a healthier, longer lifespan. The effectiveness of these compounds may also depend on genetic background, highlighting the need for further studies to explore the interactions between genetics, nutrition, and these antiaging molecules. Further research is needed to identify effective phytochemicals, understand their molecular mechanisms, and explore dose-response effects. Phytochemicals from natural sources, such as fruits, have potential not only in preventing aging but also in enhancing immunity and health, as seen during the COVID-19 outbreak.

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