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Plants and fungi metabolites as novel autophagy inducers and senescence inhibitors

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Academic Editor: Juergen Reichardt, James Cook University, Australia
Received: April 9, 2024 **Accepted:** May 23, 2024 **Published:** July 1, 2024

Cite this article: Ofir R. Plants and fungi metabolites as novel autophagy inducers and senescence inhibitors. Explor Drug Sci. 2024;2:361–8. https://doi.org/10.37349/eds.2024.00051

Abstract

Premature aging can be partially explained by inefficient autophagy (the process of cellular self-digestion that recycles intracellular components) and premature senescence (cease of cellular division without cell death activation). Autophagy and senescence are among the basic biochemical pathways in plants and fungi suggesting that some of their metabolites have the potential to act as autophagy inducers (AI) and senescence inhibitors (SI) and to inhibit inflammation and human aging. Several compounds have already been identified: trehalose and resveratrol are natural compounds that act as AI; flavonoids found in fruit and vegetables (curcumin, quercetin, and fisetin) are among the first SI discovered so far. New AI/SI can be identified using various approaches like hypothesis-driven approach for screening receptor agonists using an in-silico library of thousands of natural compounds; cheminformatics studies of phytochemicals using docking and molecular dynamics simulation, structure similarities/mimicry in vitro, "blind" high throughput screening (HTS) of libraries of natural metabolites against relevant models, and more. This article aims to promote the use of plant and fungi novel resources to identify bioactive molecules relevant for healthy aging based on the knowledge that plants and fungi use autophagy and senescence mechanisms for their own survival and homeostasis. As autophagy and senescence are interconnected, how drugs targeting autophagy, senescence, or both could contribute to healthy aging in humans will be speculated.

Keywords

Autophagy, senescence, inflammation, aging, fungi, plant, metabolites, senescence-associated secretory phenotype (SASP)

Autophagy and senescence as targets for inhibiting inflammation and aging

Autophagy is responsible for cellular self-digestion that recycles intracellular components and for trafficking events that activate innate and adaptive immunity as well as autoinflammatory diseases [1].

Senescence is the cease of cellular division without cell death activation, and immune-senescence is a series of age-related changes that affect the immune system [2], including a decline in coping with proinflammatory status [3]. Normally, functioning autophagy protects against neurodegeneration associated with intracytoplasmic aggregate-prone protein accumulation, in addition to its other roles, such as neuronal stem cell differentiation [4]. Neurodegenerative disorders share common pathogenic mechanisms, including the impairment of autophagic flux, which prevents the removal of neurotoxic misfolded proteins; effective disease-modifying strategies seek novel molecules exhibiting pro-autophagic potential [5].

Senescent cells are a major contributor to age-dependent cardiovascular tissue dysfunction and the integration of transcriptomes of senescent cell models representing multi-tissue patient samples has revealed that reduced collagen type VI alpha 3 chain (*COL6A3*) expression is one of the triggers of senescence [6]. Senescent cells represent a pharmacologic target for alleviating geriatric decline and chronic diseases [7]. Senolytic drugs like dasatinib, quercetin, fisetin, and navitoclax, were discovered using a hypothesis-driven approach; early pilot trials of senolytics suggest they decrease senescent cells, reduce inflammation, and alleviate frailty in humans [8]. Increased post mitotic senescence in aged human neurons is a pathological feature of Alzheimer's disease; senescent neurons gain an inflammatory senescence-associated secretory phenotype (SASP) and can be eliminated with senotherapeutics [5]. Microbiota sensing—free fatty acid receptor 2 signaling ameliorates amyloid-β induced neurotoxicity—can be activated by modulating proteolysis-senescence axis [9].

It has been shown that plants and fungal metabolites possess antiaging properties, and compounds isolated from plants and fungi modulate the cellular and physiological pathways that prolong lifespan and prevent age-related diseases in model organisms [10]. These compounds act through cellular processes such as autophagy and senescence and as such delay aging and prevent chronic diseases [11]. When autophagy is impaired, waste derived from tissue damage leads to organ deterioration. Thus, autophagy plays a critical role in antiaging processes and mTOR plays an important role in inhibiting autophagy. A chemo-informatics study of phytochemicals, using docking and molecular dynamics simulation, identified, among other compounds, the cyclo-trijuglone of *Juglans regia* L. as a potential ATP-competitive inhibitor of mTOR [12]. Senolytic compounds that selectively clear senescent cells, such as dasatinib, quercetin, fisetin and navitoclax, were discovered using a hypothesis-driven approach [8]; flavonoids quercetin and fisetin are found in fruits and vegetables [13] and have the potential to reduce the factors secreted by senescent cells (SASP) that lead to chronic inflammation and deterioration of healthy organs [14]. Recent in silico analysis of metabolites secreted by senescent cells may serve as tools to identify senescence inhibitors (SI) based on the mechanism of action [15].

Autophagy and senescence are interconnected

Autophagy and cellular senescence serve as stress responses to mammalian cells but the interconnection between these pathways is complex: autophagy sometimes suppress cellular senescence by removing damaged macromolecules or organelles, and in different scenarios, autophagy leads to cellular senescence and synthesis of SASPs [16]. Although autophagy and senescence interconnection may influence very different processes such as stem cells [17], aging, and cancer [18, 19], autophagy activators could be exploited to prevent the induction of senescence and drugs targeting the process of autophagy can indirectly contribute to blocking the process of senescence [18]. Autophagy and senescence converge in inducing triggers and signaling pathways such as the AMPK signaling pathway [20]. And autophagic degradation of the inhibitory p53 isoform Δ133p53α acts as a regulatory mechanism for p53-mediated senescence [21].

Autophagy regulates senescence and pathogen-induced cell death in plants [22]. This basic knowledge suggests that together, autophagy inducers (AI) and SI can contribute to healthy aging in humans through various cellular mechanisms.

Plants and fungi as resources for AI

Fungi (phytopathogenic or mycorrhizal) that interact with plants depend on autophagy as a mechanism that is responsible for recycling cell components, for the interaction of fungus-plant [23], and for affecting the pathogenicity potential of plant pathogens [24]. Several examples from the literature will be discussed below.

Plants and autophagy

Autophagy, a highly conserved self-degradation mechanism, involves the encapsulation of harmful intracellular content by double-membrane autophagic vacuoles for degradation in all parts of the plant, including roots, leaves, pollen, and more [25]. Plants must cope with diverse environmental stresses such as starvation, oxidative stress, drought stress, and invasion by phytopathogens; autophagy plays a critical role during plant differentiation, development, and aging processes [22]. The active ingredient of traditional Persian medicine, cyclo-trijuglone of *Juglans regia* L., regulates autophagy through the mTOR pathway [12]. Plant natural compounds such as curcumin, resveratrol, paclitaxel, oridonin, quercetin, and plant lectin regulate core autophagic pathways involved in Ras-Raf signaling, Beclin-1 interactome, BCR-ABL, PI3KCI/Akt/mTOR, FOXO1 signaling, and p53 [26]. The process of autophagy in plant cells at various stages of development is controlled by intracellular signaling pathways TOR kinase activity, hormone signaling, ROS levels, and changes in environmental conditions [27].

Fungi and autophagy

The growth of filamentous fungus *Aspergillus niger* in carbon-starved cultures activates autophagy genes that, probably, protect these fungi from cell death in addition to promoting nutrient recycling [28]. It has been shown that the autophagy of several fungi involves endoproteases and contributes to their pathogenicity [23]. Pathways of autophagy processes play important roles in filamentous fungal pathogenicity [24] and regulate fungal virulence and sexual reproduction in *Cryptococcus neoformans* [29] and in both the development and infection mechanisms of *Phytophthora sojae* [30].

Plants and fungi as resources for SI

Dasatinib, quercetin, and fisetin were identified as the 1st senolytic drugs derived from plants and fungi; they activate apoptosis of senescent cells and as such extend lifespan using animal models [31]. They may be effective in delaying human aging and treating chronic diseases.

Plants and senescence

Leaf senescence is accompanied by changes in physiological metabolism; regulation of leaf senescence improves resistance to biotic and abiotic stresses and delay in leaf senescence of horticultural plants improves their yields [32]. Senescence has a role in plant pathogenesis and defense: pathogens often delay senescence to keep host cells alive, and resistance is achieved by senescence-like processes in the host that involve gene transcription and biosynthesis pathways [33]. Extending the shelf-life of fresh produce and cut flowers relies on delaying cell death by lowering storage temperatures and modifying the environment to slow down metabolism and reduce the senescence and cell death-promoting effects of ethylene [34]. Screening of plants with inhibitory activity on cellular senescence showed that fruit of *Physalis angulata* L. and the aerial part of *Synurus deltoides* (Aiton) Nakai inhibited cell-senescence on HUVEC cell model, and water extracted from the root of *Polygonatum odoratum* var. *pluriflorum* for variegatum Y. N. inhibited cell-senescence in human dermal fibroblast (HDF) models. *Isatis tinctoria* L. leaf extract inhibits replicative senescence in dermal fibroblasts by regulating mTOR-NF-κB-SASP signaling [35]. Manipulation of plant senescence to improve biotic stress resistance showed that even the application of mycorrhiza can inhibit the senescence process of plants and improve their tolerance to stresses [36]. Interestingly, senescence in plants is not merely a deterioration process leading to death but rather a unique developmental state resembling dedifferentiation [37]. Several epigenetic mechanisms that control plant senescence lead to crop improvement [38]. Postharvest research challenges various materials (such as nitric oxide) for

controlling the quality of horticultural products by inhibiting senescence; interestingly, among others, hydrogen peroxide (H_2O_2) and calcium ions (Ca^{2+}) are involved [39]. Peroxidase and phenylalanine ammonia lyase are the acting players relevant to inducing senescence in plant-fungus interactions; the process is accompanied by raising the concentration of flavonoids and phenolic compounds [40].

Fungi and senescence

Mushroom extracts inhibit ultraviolet B-induced cellular senescence in human keratinocytes through augmenting sirtuin-1 (*SIRT-1*) expression [41]. Senescence has an impact on the growth of fungal colonies due to dysfunctional oxidative phosphorylation [42]. Papilla formation and hypersensitive reactions, serve as defense mechanisms against infection attempts by *Mycosphaerella* spp. (*M. graminicola*), frequently occurred in plant leaves, leading to plant senescence [43].

The publications cited here and many more suggest that plants and fungi produce metabolites that regulate autophagy and senescence and among these metabolites, there are potential AI and SI.

"The wisdom of the desert"—desert plants as novel AI and SI

Desert plants have adapted to stressful environments by synthesizing secondary metabolites and accumulating ions as osmoticum (a substance that acts to supplement osmotic pressure in a cell). Desert environments are one of the harshest places on earth due to low precipitation, limited soil nutrients, and high irradiation. The predictive metabolomics of multiple Atacama plant species unveils a core set of generic metabolites for extreme climate resilience [44]. The mechanisms to survive in harsh conditions suggest that these plants have generated unique metabolites, termed here by us "the wisdom of the desert" [45]. Studies showed variations in flavonoid metabolites along an altitudinal gradient in the desert medicinal plant *Agriophyllum squarrosum* [46]. Phytochemical analysis of secondary metabolites (alkaloids, terpenoids, tannins, saponins, flavonoids, and phenolics) in 26 plants from the desert of Egypt showed that flavonoids, phenolics, and tannins were present in all the examined species while saponin and terpenoid compounds were detected only in fifteen species. Such a resource of natural metabolites of plants, used traditionally for treatment, may be considered a new, biologically active source of medicinal compounds [47]. Among them, one can be expected to find AI and SI.

The harsh conditions of the desert also influence the biosynthesis of metabolites in fungi and microbes. Bioactive secondary metabolites from endophytic strains of *Neocamarosporium betae*, *Chaetomium globosum* (Chaetomiaceae), and *Rhinocladiella similis* collected from desert plants could be a new resource for bioactive natural products [48–50].

Filamentous cyanobacteria use unique extracellular polysaccharide-based biosynthetic pathways to survive in the desert. In addition to the extracellular polysaccharide, chaperones (to maintain protein integrity), oxidative stress protection system, synthesis of compatible solutes and ion channels, and upregulation of DNA repair mechanism are examples of the strategies cyanobacteria use for coping with desiccation/rehydration cycles in the desert [51]. These metabolites that facilitate the adaptation to extremely arid environment may contain potential AI and SI. Analysis of Sonoran desert fungi (*Aspergillus* strains) occurring in the rhizosphere of *Ambrosia ambrosoides* and in the rhizosphere of *Anicasanthus thurberi*, identified unusual new secondary metabolites terrequinone A, terrefuranone and 4R,5S-dihydroxy-3-methoxy-5-methylcyclohex-2-enone, 6-methoxy-5(6)-dihydropenicillic acid, respectively, with medicinal properties like selective toxicity against cancer cells (and not against healthy cells) [52]. These metabolites that enable growth in harsh arid environments may contain potential AI and SI.

Conclusions

Novelty: Many novel AI and SI are waiting to be discovered in plants, fungi, and microbes. As aging is characterized by systemic chronic inflammation, which is accompanied by impaired autophagy and by cellular senescence (including SASP), elimination of inflammation could be a potential healthy aging strategy. Table 1 summarizes the suggested mechanism of action of AI and SI discussed in this Perspective.

Table 1. Summary of autophagy inducers (AI) and senescence inhibitors (SI) along with their potential target mechanisms

Compounds		Target/mechanism	References
AI	Resveratrol	Sirtuin-1	[53]
	Quercetin	Ras-Raf signaling, Beclin-1 interactome, BCR-ABL, PI3KCI/Akt/mTOR, FOXO1 signaling, and p53	[26]
	Plant lectin	Ras-Raf signaling, Beclin-1 interactome, BCR-ABL, PI3KCI/Akt/mTOR, FOXO1 signaling, and p53	[26]
	Trehalose	Antioxidant and more	[54]
	Cyclo-trijuglone of *Juglans regia* L.	Inhibitor of mTOR	[12]
	Resveratrol	Ras-Raf signaling, Beclin-1 interactome, BCR-ABL, PI3KCI/Akt/mTOR, FOXO1 signaling, and p53	[26]
	Paclitaxel	Ras-Raf signaling, Beclin-1 interactome, BCR-ABL, PI3KCI/Akt/mTOR, FOXO1 signaling, and p53	[26]
	Oridonin	Ras-Raf signaling, Beclin-1 interactome, BCR-ABL, PI3KCI/Akt/mTOR, FOXO1 signaling, and p53	[26]
SI	Curcumin	Anti-inflammatory, immune-regulatory, anti-oxidative, and lipid-modifying properties	[55]
	Quercetin	Selectively clear senescent cells; reduce senescence-associated secretory phenotype (SASP); Ras-Raf signaling, Beclin-1 interactome, BCR-ABL, PI3KCI/Akt/mTOR, FOXO1 signaling, and p53	[26]
	Fisetin	Selectively clear senescent cells; reduce SASP	[8, 14]
	Dasatinib	Selectively clear senescent cells	[8]
	Navitoclax	Selectively clear senescent cells	[8]

Challenges (before moving to clinical trials in humans): i. Suitable in vitro and in vivo models are needed for screening the novel agents for toxicity/safety dosage, mode of application, efficacy, and selectivity. ii. Understanding of the underlying mechanisms linking autophagy, senescence, inflammation, and aging will enable optimization of therapeutic strategies.

Abbreviations

AI: autophagy inducers

SASP: senescence-associated secretory phenotype

SI: senescence inhibitors

Declarations

Author contributions

RO: Writing—original draft, Writing—review & editing.

Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Rivka Ofir received support from the Israeli Ministry of Innovation, Science and Technology [alona23568]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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