Clinical Summary

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Li W, et al. Emerging senolytic agents derived from natural products. Mech Ageing Dev 2019;181:1-6.

Natural Senolytics May Aid Elimination of Senescent Cells

This review distinguishes between "senolytic" and "anti-senescent" agents, and summarizes research into natural and naturally-derived compounds that exemplify each.

Age is the primary risk factor for many common illnesses, including cancer, cardiovascular and neurodegenerative disease, and diabetes. At the cellular level, one manifestation of senescence is characterized by repeated cellular injury, followed by loss of the normal ability to divide and replicate. This phenomenon may protect tissues against propagation of damaged cells, yet leaves tissues populated by zombie-like cells that no longer contribute to vital functions. Accumulation of senescent cells within tissues correlates with functional deterioration of tissues and organs, and is linked to the development of a senescence-associated secretory phenotype (SASP).

Until recently, searching for the means to limit biological aging processes has formed the core of many anti-aging investigations. However, research in the last decade strongly suggests that direct elimination of aged and dysfunctional cells may be equally as crucial as attempting to prevent aging and cumulative cellular damage. Senolytics are substances that help complete the disrupted life-and-death cycle in retained senescent cells: they allow cells to die as they would under more ideal circumstances. By reducing senescent cell burden, senolytics encourage healthier surviving cells to divide in order to aid tissue repair, rejuvenation, and remodeling.

According to the authors:

“Cellular senescence is a hallmark of aging. It is a permanent state of cell cycle arrest induced by cellular stresses. During the aging process, senescent cells increasingly accumulate in tissues, causing a loss of tissue repair capacity.”

“Genetic evidence has demonstrated that clearance of senescent cells can delay aging and extend healthspan.”

Review Summary

Senolytic activity is distinct from anti-senescent influence. Senolytics reduce the viability of senescent cells, whereas anti-senescent actions include protecting cellular integrity, improving cell redox status, and promoting cell renewal. While most senolytics to date are targeted synthetic molecules, this review focuses on natural and naturally-derived senolytic substances.

Major findings from this review include:

- While natural senolytics are generally less powerful than synthetic senolytic agents, they are food-based and demonstrate low toxicity. Examples include quercetin and luteolin.
- Natural senolytics may display tissue and cell specificity, and may be relatively potent, weak, or inactive in different types or at different sites.
- Research into natural senolytics is quite new. As yet, the flavonoid fisetin has shown the greatest versatility and potency in cells of different types. Fisetin is found in strawberries, persimmons, apples, grapes, cucumbers, and onions.
- Quercetin was identified in 2015 as a potential senolytic in multiple cell types, though its activity is modest unless combined with the drug dasatinib.
- The turmeric polyphenol curcumin has shown modest senolytic potential, and a derivative having greater bioavailability, called EF24, has shown greater senolytic activity against a variety of senescent cell types.
- Piperlongumine, an alkaloid found in the long pepper, has shown senolytic as well as cytotoxic activity in some cancer cell types, and can also influence crucial cell signaling related to cell life-and-death cycles.
- A specific extract of the goldenrod plant was found to reduce senescent human fibroblast cells by up to 30% in one study, and it also slowed the development of a senescence-associated secretory phenotype (SASP) in these cells.

This study names buckwheat as the most abundant source of D-chiro-inositol, which beneficially modulates insulin signaling pathways. Buckwheat also contains D-fagomine, which acts as a glycosidase inhibitor and may thus help limit dysregulation of the glycemic and insulinemic responses.

CONCLUSION

Many phytonutrients have shown anti-senescent properties in cells, yet few have been assayed for complementary senolytic activity. Phytonutrients found to possess both of these valuable qualities include quercetin, curcumin, fisetin, and luteolin.