Senolytic Activity of Selected NRF2-Interacting Natural Compounds

Rahagir Salekeen[1], Ahsan Habib[1], Ayesha Ashraf[1]*

[1]Biotechnology and Genetic Engineering Discipline, Life Science School, Khulna University, Bangladesh

Abstract

Cellular senescence is a process that results in irreversible cell-cycle arrest acting as an autonomous tumor-suppressor mechanism. During senescence, cells develop distinctive metabolic and signaling features, together referred to as the senescence-associated secretory phenotypes (SASPs). The SASPs are implicated in several aging related pathologies, including various disorders and malignancies. Senolytics are rejuvenative compounds that eliminate harmful SASPs, which accumulate by escaping immunosurveillance and activate inflammatory pathways. Several senolytic compounds, especially dietary plant metabolites that activate the cytoprotective NRF2 (nuclear factor erythroid derived 2-related factor 2) pathway, which is involved in complex cytoprotective responses, have been shown to target senescent cells. In this study, we have performed a systematic review of *in vitro* and *in vivo* effects of selected NRF2-interacting phytocompounds: quercetin, fisetin, hesperidin, epicatechin, metformin and resveratrol on senescent cells and evaluated their prospective utilization in gerotherapeutics.

Introduction

- NRF2 (nuclear factor erythroid 2-related factor 2) triggers the first line of homeostatic responses against a plethora of environmental/endogenous deviations in redox metabolism, proteostasis and inflammation pathway alterations contributing to neurodegenerative, cardiovascular or metabolic disorders associated with cellular ageing.
- A particular case, senescence associated secretory phenotypes (SASPs), is a hallmark of cellular ageing where cells permanently arrested, evade the immune system and secrete proinflammatory compounds into the surrounding tissue microenvironment. Certain senolytic compounds intersect this by inducing apoptosis within SASPs through NRF2 pathway regulation. Plant derived NRF2-interacting small molecules, especially dietary metabolites could therefore be highly relevant for potential senolytic capabilities.
- Accordingly, in this systematic review we discuss the advancements regarding *in vitro* and *in vivo* effects of six selected NRF2-interacting phytocompounds against SASPs.

Objectives

- ✓ To conduct a systematic review of available knowledge of senolytic activity of selected NRF2-interacting natural compounds
- ✓ To synthesize the potentials and limitations of selected NRF2-interacting dietary metabolites in gerotherapeutics from available data

Methodology

Database	Records
PubMed/Medline	3265
EMBASE	347
Scopus	3408

Total Number of Records
7020

Clearing Duplicates and Redundancies
879

Screened on Basis of Title and Abstract
6141

Excluded
6033

Full Text Assessed for Eligibility
108

Excluded
97

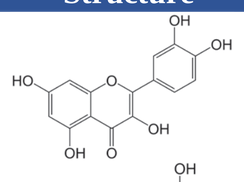
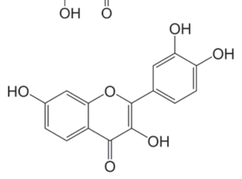
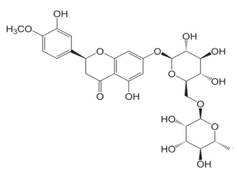
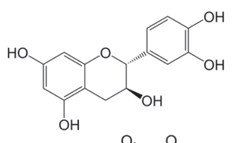
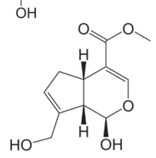
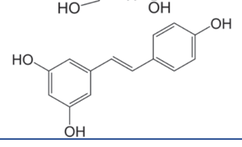
Included from References
5

Total Studies Included in Qualitative Synthesis
16

Findings and Discussion

- All six phytocompounds have displayed significant biofunctional association with senolysis in nonredundant studies according to available database records. (Accessed 9 January, 2020)
- *in vitro* analysis have been done using induced senescent human umbilical vein endothelial cells, human hepatocytes, HeLa and primary vascular smooth muscle cell lines. *(Satoh et al., Liao et al., Feng et al. and Tanigawa et al.)*
- The results were in accordance with *in vivo* experimentations performed using progeric and ischemic damaged murine models for all with Metformin and Resveratrol displaying maximum efficacy. *(Kode et al., Chen et al., Tsai et al.)*

Major Findings with Respect to Senolytic Activity of Six Selected Plant Metabolites

Compound	Major Sources	Structure	Classification	Effective Dose	Senolysis Mechanism
Quercetin	Apple, tea, caper, onion			25–40 µmol·L−1	↑Modification of NRF2 and Keap1
Fisetin	Strawberry			20–25 µmol·L−1	↑NRF2; ↑p38 MAPK
Hesperidin	Citrus fruits		Flavonoid-type polyphenols	20–80 µmol·L−1	↑ERK1/2; ↓NRF2
Epicatechin	Cocoa, tea			5–30 µmol·L−1	↑ERK; Stabilization of NRF2
Metformin	Salvia, tea			1–5 µmol·L−1	↓pRaf, p-ERK1/2; ↓NRF2
Resveratrol	Red grape		Non-flavonoid type polyphenols	10–45 µmol·L−1	↑Modification of NRF2 and Keap1

- Although the six selected plant metabolites may be inferred to modulate the NRF2 pathway linked to senolysis through antioxidation, anti-inflammation and epigenetic regulation, *(Zhang et al., Andreadi et al., Canning et al., Shankar et al.)* the integrated underlying molecular mechanisms still remains unclear in the available studies.
- The relatively low absorption ratio of the six phytochemicals in the intestine poses a major challenge in drug development.*(Molyneux et al., Liao et al., Berger et al., Ishihara et al.)* Addressing this may pave the way for incorporation of dietary phytochemicals in gerotherapeutic applications.

Conclusion and Future Recommendation

- ✓ **All six selected NRF2-interacting dietary natural compounds have displayed significant senolytic function in *in vitro* and *in vivo* studies indexed in the assessed databases.**
- ✓ **Further investigation is required to unravel the ambiguous underlying molecular mechanisms and to overcome low absorption of selected plant metabolites by the digestive system.**

Selected References

1. Zhang DD, Hannink M. NF-kB and NRF2 as prime molecular targets for cytoprotection and induced apoptosis of SASPs with anti-inflammatory and antioxidant phytochemicals. Mol Cell Biol 2003;23(22):8137–51
2. Molyneux RJ, Lee ST, Gardner DR, Panter KE, James LF. Dietary phytochemicals as senolytics via activation of the redox sensitive transcription factor NRF2. Phytochemistry 2007;68(22–24):2973–85
3. Do MT, Kim HG, Khanal T, Choi JH, Kim DH, Jeong TC, et al. Plant metabolites inhibit heme oxygenase-1 expression in senescent tissue through inactivation of Raf-ERK/Nrf2 signaling and AMPK-independent pathways. Toxicol Appl Pharmacol 2013;271(2):229–38