Quest for Bioactive Compounds in Our Diet with Anti-Ageing and Anti-Aggregation Properties †

Nikoletta Papaevgeniou, Eleni Panagiotidou, Konstantina Filippopoulou and Niki Chondrogianni *

Institute of Biology, Medicinal Chemistry and Biotechnology, National Hellenic Research Foundation, 48 Vassileos Constantinou Avenue, 116 35 Athens, Greece; npapaevgeniou@eie.gr (N.P.); epanagiotidou@eie.gr (E.P.); konphil.biol@gmail.com (K.F.)

* Correspondence: nikichon@eie.gr; Tel.: +30-210-727-3768
† Presented at Natural Products and the Hallmarks of Chronic Diseases—COST Action 16112, Luxemburg 25–27 March 2019.

Published: 29 April 2019

Abstract: Ageing is a complex process affected by both genetic and environmental factors, characterized by a gradual failure of functionality, reduced stress response and resistance, leading to enhanced probability for age-related diseases and mortality. During the last decades, natural compounds have attracted the attention of researchers in the quest of bioactive phytochemicals with anti-ageing properties. For a few of these compounds an extra advantage appears; many of them have been shown to decelerate the progression of age-related diseases with emphasis on aggregation-related diseases. Using the nematode *Caenorhabditis elegans* along with the replicative senescence model of human primary fibroblasts, we have identified compounds that are part of our diet with anti-oxidation, anti-ageing and anti-aggregation activities. Some of the identified compounds promote their anti-ageing activity through activation of the proteasome, others through the activation of Nrf2 transcription factor, while others through inhibition of glucose transporters (GLUTs). Our work identifies new bioactive compounds with anti-ageing and/or anti-aggregation properties or reveals additional beneficial properties on already known bioactive compounds.

Keywords: anti-ageing; anti-aggregation; anti-oxidation; bioactive compounds; proteasome; Nrf2; glucose transporters

1. Introduction

Ageing is a multi-factorial, complex process affected by both genetic and environmental factors. It is characterized by a gradual failure of functionality, reduced stress response and resistance, leading to enhanced probability for age-related diseases and eventually mortality [1]. Natural compounds have attracted the attention of multiple labs world-wide due to their multiple beneficial properties (anti-oxidant, anti-ageing, anti-inflammatory, among others), their variety and of course their natural origin that makes them more accessible. If they are also part of the normal diet, the side-effects are further diluted out.

Human primary fibroblasts perform a certain number of population doublings before they enter a state of irreversible growth arrest where they accumulate a series of different characteristics (morphological, biochemical, physiological etc.) that clearly distinguish them from their young counterparts. This is known as the replicative senescence model [2]. The nematode *Caenorhabditis elegans* is a multi-used organismal model with ideal features for ageing (and age-related diseases) studies; it is inexpensive to maintain and grow in the laboratory, it has a short life cycle and lifespan, it has multiple readouts, it is frequently used for screening of compounds and ~80% of nematode
genes have human homologs while numerous human diseases have been modelled and studied in *C. elegans* [3].

Using the above-mentioned model, our lab has identified compounds that are part of our diet with anti-oxidation, anti-ageing and anti-aggregation activities.

2. Anti-Ageing Compounds

Proteostatic mechanisms and especially the proteasome, are highly affected by ageing [4] while loss of proteostasis features among the hallmarks of ageing [1]. Activation of the proteasome either through genetic means or through natural compounds has been suggested as a promising anti-ageing strategy [5]. We have therefore sought to identify compounds that are part of normal diet with proteasome activating properties. Oleuropein, the olive constituent [6], quercetin [7] and 18α-glycyrrhetinic acid [8,9] are few of the natural compounds that we have identified as proteasome activators and were shown to extend cellular and organismal lifespan.

We have also identified natural compounds with anti-ageing properties that do not affect the proteasome. A minor component of silymarin that is used in a plethora of dietary supplements, namely 2,3-dehydrosilybins A/B (DHS A/B), was shown to promote cellular and organismal lifespan extension on top of its already known anti-oxidative and neuroprotective properties [10]. Using *C. elegans*, we revealed that this extension is FGT-1 (facilitative glucose transporter)-dependent; FGT-1 has been suggested as the GLUT (glucose transporters) paralogue in the nematodes.

3. Anti-Aggregation Compounds

Ageing is a major risk factor for the manifestation of human diseases including neurodegenerative diseases [11]. Amelioration of healthspan is predicted to exert beneficial effects on the progression of diseases as well. Specifically, if we refer to aggregation-related diseases like Alzheimer’s disease (AD) where aggregates accumulate due to dysfunctional proteostatic mechanisms [12], anti-ageing compounds that have been isolated for their proteasome-activating properties are expected to exert positive action is conditions of such disease. Indeed, 18α-glycyrrhetinic acid that has been identified as a proteasome activator [8] was found to exert anti-aggregation activity in the context of a multicellular organism (*C. elegans* model for AD) but also in human and murine cells of nervous origin [9].

Similar positive action was shown for DHS A/B [10] that was identified as an anti-ageing compound in the absence of effects on proteostatic mechanisms. Its anti-oxidant activity is probably playing a major role in the observed protective effect against aggregation.

4. Conclusions

Nature offers a huge inventory of compounds with multiple structures and activities that may be used in anti-ageing and/or anti-aggregation applications. What is still missing is extensive investigation on the pathways that are involved in the observed beneficial phenotypes. Nevertheless, results to date are encouraging and suggest that cellular ageing might be decelerated.

**Funding:** Research from N.C. lab is currently co-financed by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH—CREATE—INNOVATE (project code: T1EDK-00353 and T1EDK-01610) as well by the project “STHENOS-b” (MIS 5002398), which is funded by the Operational Programme “Competitiveness, Entrepreneurship and Innovation” (NSRF 2014-2020) and co-financed by Greece and the EU (European Regional Development Fund). NC lab is supported from COST Action NutRedOx-CA16112 supported by COST (European Cooperation in Science and Technology).

**Conflicts of Interest:** The authors declare no conflict of interest.
References

1. Hayflick, L. The limited in vivo lifetime of human diploid cell strains. *Exp. Cell Res.* 1965, 37, 614–636.
2. Apfeld, J.; Alper, S. What can we learn about human disease from the nematode *C. elegans? Methods Mol. Biol.* 2018, 1706, 53–75.
3. Lopez-Otin, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The hallmarks of aging. *Cell* 2013, 153, 1194–1217.
4. Papaevgeniou, N.; Chondrogianni, N. UPS Activation in the battle against aging and aggregation-related diseases: An extended review. *Methods Mol. Biol.* 2016, 1449, 1–70.
5. Chondrogianni, N.; Voutetakis, K.; Kapetanou, M.; Delitsikou, V.; Papaevgeniou, N.; Sakellari, M.; Lefaki, M.; Filippopoulou, K.; Gonos, E.S. Proteasome activation: An innovative promising approach for delaying aging and retarding age-related diseases. *Aging Res. Rev.* 2015, 23, 37–55.
6. Katsiki, M.; Chondrogianni, N.; Chinou, I.; Rivett, A.J.; Gonos, E.S. The olive constituent oleuropein exhibits proteasome stimulatory properties in vitro and confers life span extension of human embryonic fibroblasts. *Rejuvenation Res.* 2007, 10, 157–172.
7. Chondrogianni, N.; Kapeta, S.; Chinou, I.; Vassilatou, K.; Papassideri, I.; Gonos, E.S. Anti-ageing and rejuvenating effects of quercetin. *Exp. Gerontol.* 2010, 45, 763–771.
8. Papaevgeniou, N.; Sakellari, M.; Jha, S.; Tavernarakis, N.; Holmberg, C.I.; Gonos, E.S.; Chondrogianni, N. 18α-glycyrrhetinic acid proteasome activator decelerates aging and Alzheimer's disease progression in *Caenorhabditis elegans* and neuronal cultures. *Antioxid. Redox Signal.* 2016, 25, 855–869.
9. Kapeta, S.; Chondrogianni, N.; Gonos, E.S. Nuclear erythroid factor 2-mediated proteasome activation delays senescence in human fibroblasts. *J. Biol. Chem.* 2010, 285, 8171–8184.
10. Niccoli, T.; Partridge, L. Ageing as a risk factor for disease. *Curr. Biol.* 2012, 22, R741-52.
11. Upadhya, S.C.; Hegde, A.N. Role of the ubiquitin proteasome system in Alzheimer's disease. *BMC Biochem.* 2007, 8, S12.
12. Filippopoulou, K.; Papaevgeniou, N.; Lefaki, M.; Paraskevopoulou, A.; Biedermann, D.; Kren, V.; Chondrogianni, N. 2,3-Dehydroisilybin A/B as a pro-longevity and anti-aggregation compound. *Free Radic. Biol. Med.* 2017, 103, 256–267.

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).