



## Abstract

# Quest for Bioactive Compounds in Our Diet with Anti-Ageing and Anti-Aggregation Properties <sup>†</sup>

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**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 18 $\alpha$ -glycyrrhetic 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-dehydrosilybin 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 in conditions of such disease. Indeed, 18 $\alpha$ -glycyrrhetic 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.

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