ABSTRACT

STUDY OF NATURAL COMPOUNDS FROM MACROALGAE OF THE EASTERN MEDITERRANEAN BASIN WITH ANTI-AGING ACTIVITY AND PROPERTIES AGAINST AGE-RELATED DISEASES

Aging is a normal, dynamic, multidimensional and irreversible process in which many modifications occur at all levels and forms of life (molecular, cellular and organismal). These progressive changes pose an increased risk of developing accidental pathology and age-related diseases that eventually lead to death. The study of the phenomenon of human aging and age-dependent diseases is facilitated by the use of cellular aging models such as the model of replicative senescence as well as animal models such as the nematode worm, *Caenorhabditis elegans*.

In recent years, increasing number of studies are focused on natural products and their active compounds that may delay the progression of aging and age-related diseases. Earlier studies of the Molecular Aging Laboratory of the National Hellenic Research Foundation have revealed natural compounds with anti-aging activity and some of those have already been used in the production of anti-aging cosmetic series. The term "pharmaco-nutrient" (or otherwise called pharmaceutical food products) has emerged in recent years and refers to nutrients, dietary supplements and plant products that present additional health benefits beyond their basic nutritional value as foods. A wide range of pharmaceutical food products has been shown to affect the immune system status and sensitivity/susceptibility to certain diseases, and there are indications of positive effects on oxidative stress-related diseases, including Alzheimer's disease (AD). There are various categories of compounds that could be characterized as potential pharmaceutical food products, including polyphenols, triterpenes, phenols and carotenoids that share antioxidant, anti-aging and anti-inflammatory properties.

Although the land flora has been the subject of research for many years, the marine flora and fauna are less studied and the interest is now turned towards that direction. Some components of marine organisms have already been reported with antioxidant, anti-inflammatory and anti-aging properties and the fact that they exhibit unusual chemical structures that endow them with new properties, makes them even more interesting. Moreover, various marine compounds have been shown to have much more pronounced antioxidant properties than components of the land's vegetal wealth. Finally, marine organisms also produce molecules with potential photo-protective properties and action against photo-aging. The combination of all the above protective effects that can be attributed to factors and components of marine flora and fauna highlights the importance of investigating and exploiting these organisms in the field of anti-aging and cosmetology as well as in the field of pharmaceuticals.

The aim of the proposed PhD thesis is the identification of natural compounds from macroalgae of the Eastern Mediterranean basin with anti-aging activity and properties against protein aggregation and the related diseases. The effects of these compounds will be studied: 1) in the modification of the cellular lifespan (model of replicative

senescence), 2) in the modification of the organismal lifespan (*C. elegans*), and 3) in the induction and progression of age-dependent diseases, such as AD.

Metabolites of various chemical groups from a library of fully characterized substances isolated from Mediterranean benthic organisms will be scanned for their ability to extend organismal life expectancy (*C. elegans*). Mutants for pathways that regulate aging will be used to reveal the mechanisms of action of each metabolite. The optimal concentration of these metabolites will be administered: 1) to primary human fibroblasts and their cellular lifespan will be measured (model of replicative senescence) and, 2) to nematode strains that are models for AD. More specifically, the strains CL4176 and CL2331 will be used. CL4176 strain expresses the human Aβ peptide in its body wall muscle cells and it gets paralyzed upon Aβ accumulation. CL2331 strain expresses the human Aβ peptide linked to GFP (Green Fluorescent Protein) in its body wall muscle cells; this strain will be used to visualize Aβ aggregates *in vivo* by confocal fluorescence microscopy.

In total, in the context of this thesis, natural compounds with anti-aging and anti-protein aggregation activity will be identified to reveal compounds that can potentially serve as pharmaco-nutrients. Since both aging and aggregate formation during AD progression are the final irreversible points, pharmaceutical food products have the advantage that being taken through normal nutrition from young ages, they can block/delay the initial stages of the two phenomena before the aging phenotype even appears and before the disease becomes apparent. Consequently, these compounds may act protectively and may serve in the deceleration of the disease establishment and/or progression.

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METHODS THAT WILL BE USED: Cell cultures, *C. elegans* cultures, detection of oxidized proteins, detection of reactive oxygen species (ROS), oxidative stress resistance tests, RNA and protein extraction, Real Time PCR, Immunoblotting, among others.

KEYWORDS: *C. elegans*, lifespan, replicative senescence, pharmaceutical food products, anti- oxidant, ROS, macroalgae, Aβ peptide, Alzheimer's disease, aging, marine compounds.

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