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# Extract from *Saussurea Involucrata* is a Promising Route for Slowing Down Organismal Aging

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## ABSTRACT

Aging is the final act of life, characterized by progressive decline tissues and organs functions and increased risk of mortality. Organismal senescence is a multifactorial process which difficult to quantitate. Each measurable physiological function decreases at a specified speed in a wide range. Aging is phenomenon not coded in the genome. Accumulating evidence links senescence to epigenetic alterations. Given the reversible nature of epigenetic mechanisms, these pathways provide promising avenues for therapies against age-related phenomenon and diseases. In this mini review the potential therapeutic benefits of *Saussurea involucrata* extract on organismal senescence is addressed. Data provide renewed insight on the molecular modes of protection by extract from *Saussurea involucrata*, which is likely to be at least in part mediated not only by her potent antioxidant and anti-inflammatory effects. We identify processes affecting organismal senescence and suggest some reasonable proposals for the future research including possible prevention, slowdown or treatment of aging phenomenon. In conclusion, this review aims to highlight the therapeutic significance of the *Saussurea involucrata* and gives guidance on future research of this plant in organism aging.

**Keywords**: Aging, organismal senescence, cell senescence, *Saussurea involucrate,* prevention, treatment

## INTRODUCTION

Aging in mammals is universal and degenerative, and appears to be unavoidable even in very sheltered environments. Aging is a multifactorial action, which is difficult to quantify. Every measurable physiological action decreases with characteristic speed over a wide range. Therefore, when looking for the cause of mammalian aging, it is reasonable to look for an intrinsic process that damages intracellular organelles, which limits lifespan. Senescence is a final outcome of life, characterized by progressive decline in tissues and organs function and increased risk of mortality. Aging is the gradual loss of molecular accuracy following reaching maturity, culminating in loss of function and ultimately illness and death. In most organisms, the rate of aging is inversely proportional to lifespan. Accelerated aging is also the risk factor for development cancer, cardiovascular disease and neurodegeneration [1-3]. On the other hand, healthspan is defined as the time for which an organism remains free of diseases. Identifying pathways to increase healthspan and lifespan are intriguing challenges of biogerontology research. Senescence is now the most common and cost problem in the world. The number of aged people actually is growing very fast especially in developed countries. Above is a major cause of progressing adult disability worldwide for which is recently no effective prevention. Geriatric specialists are hunting for safe and effective substances to slow down senescence as many cases as possible.

### Organismal Aging

Aging is not coded in the genome, is associated with epigenetic mechanisms, which limit vital activities [4]. During aging, spare parts age, largely as a result of progressive loss of vital activities, some functions disappearing quick and other relatively slow, as for example elastic functions of blood vessel elasticity or accommodation [5-7]. The slowest disappearance of function is connected with the speed of nervous conductivity but the fastest with elastic recoil [5,7].

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Rapidly declining elastic functions, such as accommodation, skin, vascular and pulmonary elasticity, concern essential physiological functions in organism. Some aging processes are not the result of loss of function, but they are the consequence of illegitimate biochemistry in the organism, without running defenses mechanisms, such as non-enzymatic glycosylation. The loss of vital activities can be slow, intermediary and/or rapid [5,7]. Aging in spare parts is the consequence of uneven disappearance of individual functions, dependent on cellular and molecular mechanisms involved, mainly mediated by receptors [5,8]. It has been shown that the density of receptors on cells decreases with age [5]. Not which receptors, such as receptor recognizing elastin, lose the properties of signal transmission to intracellular compartment, although the receptor on the cell membrane is present [5,6]. In contrast to aging, age-related pathologies are under the control of genes that react to stress/pathogens and maintain the genome [5].

**Cellular Senescence**

Cell death is probably caused by poisonous body factors during stress. Cultures with human skin fibroblasts have been shown that dividing of the cell culture stopped reaching 50 to 60 doublings [5]. It means that cells life in culture is limited. Similar data were obtained with organ cultures [5]. Searching for mechanisms limiting cell viability in culture indicated progressive shortening of telomeres necessary to attach polymerase DNA copying genes for cell duplication [9]. This mechanism is not enough to explain the aging of the organism. Confirmation of the above suggestion is loss of human skin, determined by images analysis of histological sections which was faster than telomere loss [5,10]. Proteolysis is upregulated with age, at the cell, tissue and organ level, contributing to the age-dependent disappearance of skin tissue and slows down with age cell proliferation. [5].

Definition of cellular aging associated with the pathophysiological process in which cells permanently lose their proliferative capacity, maintaining viability and metabolic activity [11,12]. Senescent cells characterized by flattening, enlargement of cell and nucleus, intracellular vacuolization and changed chromatin structure. At the biochemical level, cellular senescence is characterized by: (1) increased lysosomal galactosidase beta 1 activity, (2) absence of marker of proliferation Ki-67, (3) inhibition of multiple cyclin-dependent kinases and consequent dephosphorylation of various members of the retinoblastoma protein family [13], (4) activation of the DNA damage machinery, generally as a consequence of telomere erosion, and (5) presence of so-called senescence-associated heterochromatic foci [11,14,15]. Aging cells secrete a diversity of mitogenic and immunomodulatory cytokines, chemokines and growth factors [15,16]. Senescence-associated secretory phenotype appears to be involved in the immunological clearance of aging cells, it also affects the function of neighboring cells [1,15-17].

Cellular aging processes contribute to the development of embryogenesis [18] and to many pathophysiological operations, including tissue repair and regeneration, immunity, stem cell compartment maintenance and overproduction [19-25]. In particular, cellular aging occurs in response to: (1) potentially carcinogenic events including oncogene activation or oncosuppressor gene inactivation, and (2) several sublethal cellular actions, including DNA damage, telomere shortening, stalled DNA replication, dysfunction of mitochondria, metabolic, mitotic, lysosomal, mechanical, oxidative or proteotoxic activities [2,14,26]. Evidence indicates that senescent cells collect during organismal aging due to their increased formation coupled to ineffective clearance [3,12,15,27]. Therefore, chronic cellular aging has been involved in personal aging, tissues deterioration, lifespan shortening and the etiology of different age-related diseases, such as neurodegeneration [1,12,19,28-34]. Thus, organismal senescence is an attractive treatment target for extension lifespan [15,35].

**Brain Aging**

The triggers of aging are incompletely understood but may include the free radical hypothesis of aging [36], which quickly evolved to the so-called mitochondrial hypothesis of aging [37]. In an age-related changes in the brain, the hippocampus is one of the most vulnerable areas. Brain aging shows different phenotypes, such as a slow progressive loss of pyramidal neurons in hippocampus and their connections, increased oxidative stress, a reduction in neurogenesis and behavioral deficits [38,39]. In generally aging changes the connections between the neurons in the hippocampus network. In the brain the most sensitive parts to oxidative stress include the hippocampus, brain cortex and striatum. The solid correlation between increasing age and the development of oxidative damage of neurons has generally supported the oxidative stress theory of aging [36]. In addition neurogenesis is severely decreased in the part of hippocampus called dentate gyrus [40] and this is strongly associated with cognitive decline. The aging of people is accompanied by chronic low-grade inflammation, a phenomenon associated with weakness, morbidity and mortality in the elderly [41]. This condition is associated with the accumulation of senescent cells in aging tissues and organs through the aging-related secretory phenotype, which includes key pro-inflammatory cytokines [41].

Amongst the genetic effects of longevity, it should be mentioned the extraordinary impact of mTOR on organismal aging, which increased longevity in mice even at a comparatively advanced age, suitable to middle-aged people [42]. Other interesting example concerns genes associated with autophagy, which control insulin – insulin receptor-

mediated-response [43]. Gender-determining genes were either shown to be important in the inheritance of longevity [44]. Some drugs were also shown to act on longevity, among them N-acetyl-L-cysteine in Caenorhabditis elegans [45] and metformin on peripheral mononuclear cells from patients with prediabetes [46]. It has also been shown that some herbal supplements prolong the life span of Drosophila melanogaster under certain environmental conditions and increase even resistance to stress [5].

**Experimental Model of Aging**

D-galactose is a naturally occurring molecule in the human and animal body and different investigations have demonstrated that reactive oxygen species can be produced during the course of D-galactose metabolism [39,47]. Chronic administration of D-galactose is reducing sugar that can generate advanced glycation end products, neurodegeneration and age-related phenotypes [39,47]. Moreover, the administration of D-galactose to experimental animals significantly decreases proliferation of progenitor cells, reduces the migration and survival of new neurons in dentate gyrus [38]. Above alterations of hippocampus neurogenesis is analogous to that observed in normally aging mice and/or human [48].

Although aging science is flourishing, the puzzles of this process have not yet been fully solved and preventions have not been found. Senescence is a top priority for rich countries and many corporate pharmaceutical portfolios and long-term strategies and is actively targeted by different biotechnological companies, making aging one of the most investigated processes in the pharmaceutical industry. The discovery regarding the removal of p16Ink4a-positive senescent cells which delay aging-associated diseases in genetically modified mice opens interesting perspective regarding treatments approaches aimed at the removal of aging cells to prevent or delay tissue and/or organ dysfunction [28]. However, aging cells may also exert a physiological role and they can come in handy as demonstrated during wound healing [24] and their removal could have adverse effects, especially in young organisms [21]. For these reasons, it is necessary to intensify studies efforts to clarify the role of selective removal of changed by aging cells in experimental models which mimic old organisms. In this context, the progress of strategies to clean senescent cells from tissues could represent a new tool for the restraint chronic inflammation in aging population and ameliorate people healthy lifespan. Now a feasible approach may be use of senolytic substances [49], in particular natural bioactive molecules, such as quercetin or flavonoids, which might be easily used in human clinical trials, and minimizing the risk of adverse effects [50,51]. The natural diet supplementation for aging and diseases connected with aging has currently received a great deal of attention in industry and lay and medical communities. There had been much enthusiasm because aged individuals tolerated the supplementation very well, without dangerous side effects.

**Asian Traditional Medicine and Aging**

Lastly additional attention in the industry of new medicine discovery has been pointed on the neuroprotective action of natural Asian traditional medicine known for thousands of years. Natural molecules with the effects of calcium stabilization, antiinflammation, antiapoptotic and antioxidant show preventive and therapeutic effects on aging associated disease and exhibit the promising targets [52,53]. Current approaches paying attention on the possible capacity of natural substances derived from vegetables, fruits, beverages, plants and herbs to prevent or treat mainly age related injuries with dementia phenotype [52-58]. Based on the knowledge from folk Chinese medicine, which presented that *Saussurea involucrata* has the effects of warming the kidney, activating yang, expelling wind, eliminating dampness, inducing menstruation and promoting blood circulation and has been used for treatment rheumatoid arthritis, impotence, irregular menses, cough with cold, stomachache and altitude sickness [59]. Yang et al. [51] proposed to verify protective effects of this substance in aging. To support above currently some natural neuroprotective substances from extract of *Saussurea involucrata* have been demonstrated to be effective in focal brain ischemia [60] and epilepsy produced by pentylenetetrazol [61], diseases which frequently occurring in adults and in this situation an innovative methodological trial design was introduced by Yang et al. [51]. The data from Yang et al. [51] study demonstrate that extract from *Saussurea involucrata* reduces aged brain damage by antioxidant activity [61]. This data are supported by protective effects of extract from *Saussurea involucrata* in epilepsy [61]. Above studies suggest that extract from *Saussurea involucrata* may be a beneficial nutrient for the slowing down senescence and lifespan extension. In this situation extract from *Saussurea involucrata* is a vital source of dietary antioxidants [62]. Else physical activity together with natural neuroprotection trials seems today to be feasible in clinical care of aged humans.

**DISCUSSION**

Aging is an unavoidable outcome of life, presented as progressive decline in cell, organ and tissue activity and raised risk of mortality. Increasing evidence links aging to epigenetic changes [4]. Known the reversible nature of epigenetic processes [4], these mechanisms give promising avenues for therapy against age-related pathology and disappearance of function. In this mini review of aging we tried to present current search advance in possible therapy of phenomenon, focusing on prevention, slowdown and treatment options by natural supplementation. It is evident that the present increase in human life expectancy and slowing aging is the result of medical knowledge and social-

economic progress. Especially, direct manipulation of epigenetic factors will greatly advance our understanding of the role of epigenetic changes that are causal to aging. Together with the new technologies, and new experimental models in aging research will provide key insight into the epigenetic mechanisms that underlie aging and will likely identify factors and pathways that can be targeted to improve health and lifespan in aged humans. In this mini review, we have presented the possible protective activity and the mechanism of action by extract from *Saussurea involucrate* against aging processes. Use of this herb independently or in combination it should be clarified. The exact quality control as well as the toxicology investigations is necessary to guarantee the safety use this herb in human clinic. Use *Saussurea involucrate* decreased the expression of cyclooxygenase-2 via down regulation of NF-kappaB, resulting in a decrease in lipid peroxidation. These data also showed that oral administration of extract from *Saussurea involucrate* to mice significantly improved behavioral performance [51] and these results suggest that *Saussurea involucrate* exerts potent anti-aging effects via antioxidative mechanisms and also maintained endogenous antioxidant enzymatic activities stabilizing mitochondrial activity [62]. Presented results should encourage further investigation into the potential use of *Saussurea involucrate* for the prevention, slowdown and treatment e.g. neurological diseases and physical fatigue [55-58,63].

### Future Perspectives

In summary development of neuroprotective substances from traditional Asian medicine and some nutrient plant like *Saussurea involucrata* is a promising route in the slowing down of neuropathological changes in aged brain and associated with age neurodegenerative symptom like dementia. In the future additional interest should be paid to above agents how and when they can cross easily blood-brain barrier and clear pathological targets without or with fewer side effects. The exponential progress in traditional medicine herbs, vegetables and plants in the slowing down senescence and lifespan extension with additional new information from Yang et al. [51] study about neuroprotective extract from *Saussurea involucrata* in aging mouse model made in the last decade provides the potential to achieve this goal. Further investigations are necessary to evaluate the effect of *Saussurea involucrata* on retention of memory and to determine the precise mechanisms of action. We hope that presented data can provide a research program through a new interpretation of *Saussurea involucrata* biology to identify, which deleterious mechanisms are most central to the initiation of the aging process and in this way lead us gradually to a final causal theory, prevention and slowing aging. In this context, the progress of strategies to remove aging cells could represent an emerging tool for the damping of chronic inflammation and to extend human lifespan. An applicable approach may be the use of senolytic compounds [49], in particular natural bioactive substances, such as phenylpropanoids, flavonoids, coumarins, lignans, sesquiterpenes, steroids, ceramides, polysaccharides and rutin, which are isolated from *Saussurea involucrata,* and which might be easily used in clinical trials, while minimizing the risk of adverse effects [50,51,62]. Although studies have confirmed that *Saussurea involucrata* has a broad range of bioactivities, further in-depth studies on the exact bioactive molecules and the mechanism of action are expected.

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