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Polysaccharides from Medicinal Herbs As Potential Therapeutics for Aging and Age-Related Neurodegeneration

Haifeng Li,[1,2] Fangli Ma,[2] Minghua Hu,[2] Chung Wah Ma,[2] Lingyun Xiao,[3] Ju Zhang,[3]
Yanxia Xiang,[3] and Zebo Huang[1]

Abstract

Recent studies have uncovered important aging clues, including free radicals, inflammation, telomeres, and life span pathways. Strategies to regulate aging-associated signaling pathways are expected to be effective in the delay and prevention of age-related disorders. For example, herbal polysaccharides with considerable anti-oxidant and anti-inflammation capacities have been shown to be beneficial in aging and age-related neurodegenerative diseases. Polysaccharides capable of reducing cellular senescence and modulating life span via telomere and insulin pathways have also been found to have the potential to inhibit protein aggregation and aggregation-associated neurodegeneration. Here we present the current status of polysaccharides in anti-aging and anti-neurodegenerative studies.

Introduction

As a fundamental law of life, aging is a time-dependent process characterized by cumulative lesions of physiological systems, leading to functional decline and increasing risk of death.[1] During this process, the essential functions of living cells and tissues are weakened due to chronic damage from external as well as internal stresses, ultimately causing various diseases such as neurodegenerative diseases, atherosclerosis, and cancer. Conversely, these age-related disorders also cause deterioration of physiological integrity and promote the pathological aging process. The degenerative nature of aging affects all living organisms irreversibly and has severe social and medical consequences for human beings as the aging population grows. Therefore, the possibility of delaying aging and thus alleviating age-associated disabilities has attracted extensive attention from biomedical scientists as well as ordinary people throughout the history of humankind. Traditional Chinese medicine, for instance, has a long history of aging-related studies, and hundreds of Chinese herbs have been used during the centuries to delay aging and treat age-related diseases. In *Shen Nong's Herbal Classics* (Shen-Nong-Ben-Cao-Jing, ~ 110 BC) alone, about 100 herbs were recorded to have therapeutic potentials in aging-associated conditions. Intriguingly, recent studies have shown that the pharmacological activities of polysaccharides from traditional anti-aging Chinese herbs play a role in aging-associated conditions, including life span–extending and neuroprotective effects, suggesting their beneficial potential in aging and age-related diseases.

Retardation of Aging Process by Herbal Polysaccharides

A number of hypotheses, *e.g.*, free-radical and telomere theories, have been proposed in the last few decades in seeking to unravel aging. Although none of the existing hypotheses can fully explain the aging process, growing information on molecular mechanisms of aging has accumulated from diverse animal models, including the nematode *Caenorhabditis elegans*.[2] It has now been widely accepted that aging involves a range of biochemical pathways, including oxidative stress, telomere and telomerase, the insulin/insulin-like growth factor-1 signaling (IIS) pathway, target of rapamycin (TOR), and dietary restriction.[3] These pathways interact with each other and form a balanced network under normal, tolerable stresses. However, molecular homeostasis of the network may be interrupted as extrinsic and intrinsic stresses accumulate during aging progression (Fig. 1).[4] Therefore, therapeutics capable of balancing the aging-associated network are expected to maintain molecular homeostasis and thus delay aging and age-associated pathogenesis.

[1]Guangdong Province Key Laboratory for Biotechnology Drug Candidates, School of Biosciences and Biopharmaceutics, Guangdong Pharmaceutical University, Guangzhou, China.
[2]Research & Development Centre, Infinitus (China) Company Ltd., Guangzhou, China.
[3]School of Pharmaceutical Sciences, Wuhan University, Wuhan, China.

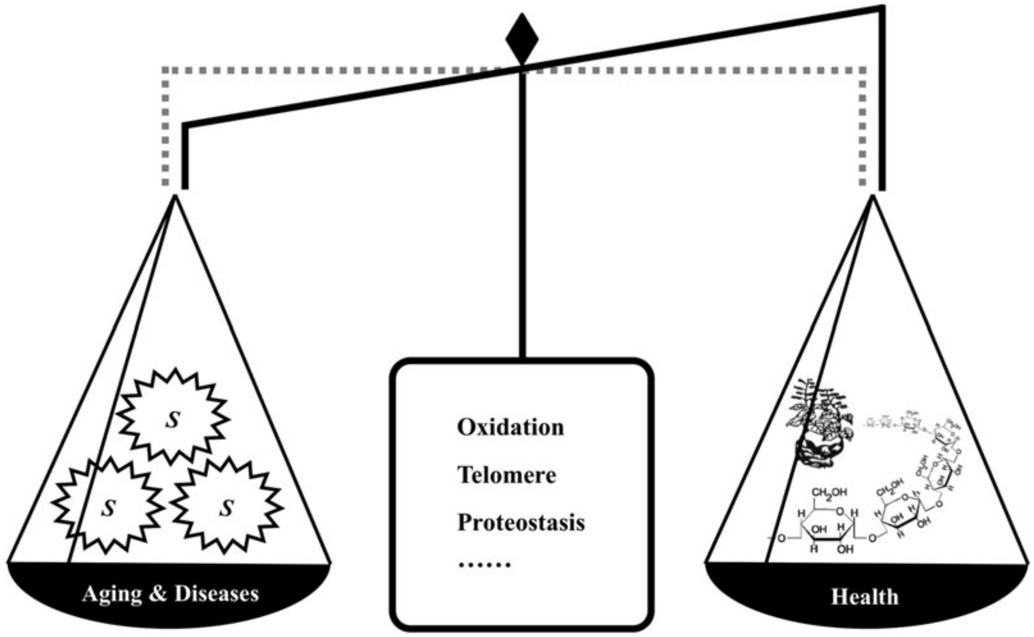

FIG. 1. Pharmacological intervention of aging and age-related diseases by herbal polysaccharides. Aging as a complex process is affected by a variety of molecular pathways, *e.g*., oxidation, telomere, proteostasis, nutrient metabolism, and inflammation. As aging progresses, both extrinsic and intrinsic stresses accumulate, tipping the cellular balance of organisms to aging and aging-associated diseases (solid black line). Nevertheless, herbal polysaccharides able to regulate aging-related signaling pathways may be used to counteract the detrimental stresses and rebalance the impaired homeostasis toward a healthy state (dashed gray line). S, stress.

Although most work related to herbal polysaccharides has focused on their anti-tumor and immunoregulatory effects, emerging evidence has revealed their anti-aging activities. For example, oxidative stress initiated by increased level of reactive oxygen species (ROS) is a major trigger of the aging process and age-related pathogenesis,[5] but both cellular ROS levels and oxidative damages can be reduced by polysaccharides. For example, the polysaccharides from *Nostoc commune* can scavenge ROS *in vitro* and reduce paraquat toxicity in *C. elegans* by modulation of malonaldehyde content and anti-oxidant enzyme activities.[6] The polysaccharides from *Angelica sinensis*, a herb traditionally used as a blood-activating medicine, not only protects cultured neural cells from hydrogen peroxide (H_2O_2)-induced cytotoxicity and reduces elevated intracellular ROS but also prevents *in vivo* oxidative damages and ameliorates ischemic brain injury in rats.[7]

In addition to oxidative stress, telomere and telomerase are also known to play an important role in keeping cellular proliferation potential and averting replicative senescence. Telomerase is generally needed to maintain the sequence of the telomere, but most mammalian somatic cells lack telomerase, leading to the continuous loss of telomere length.[8] Although telomere attrition is an inevitable event of aging cells, the aging process can be retarded by experimental introduction or reactivation of telomerase.[8] For example, the polysaccharides from *Cistanche deserticola* have recently been shown to increase telomerase activity in heart and brain tissues of aged mice.[9] The polysaccharides from *Astragalus membranaceus*, another well-known traditional Chinese herb, are able to increase telomerase reverse transcriptase gene expression and inhibit zebrafish cell apoptosis and senescence.[10] Interestingly, however, some polysaccharides are also reported to impair the telomere region or inhibit telomerase activity to exert an anti-tumor effect.[11] Paradoxically, reducing high telomerase activity of tumor cells may actually contribute to the delay of organismal aging and associated diseases.[8] Therefore, these studies not only demonstrate the capability of herbal polysaccharides to regulate telomere length and telomerase activity, but also suggest that their modes of action are dependent on specific disease contexts.

Because the aging process is time-dependent, life span is undoubtedly an important index to reflect the extent of senescence. In addition to telomere and telomerase, several signaling pathways also participate in life span regulation. IIS, for instance, is an evolutionarily conserved pathway that regulates organismal metabolism and development as well as life span, as demonstrated in animal models. It has been shown that constitutive down-regulation of IIS intensity depresses cell growth and metabolic rate, and consequently reduces the possibility of cellular damage, which is somehow favorable to longevity.[1] Recent studies have also proved that both genetic manipulation and pharmacological intervention of the IIS pathway can extend the life span of nematodes, flies, and mice. For example, the polysaccharides from *Ganoderma lucidum* are able to extend life span in *C. elegans* via a pathway involving DAF-16 (a DAF-2/IIS downstream component) and PMK-1 (p38 mitogen-activated protein kinase [MAPK]).[12] Another example is astragalan, a polysaccharide isolated from *A. membranaceus* roots, which is shown to extend the life span of *C. elegans*, including wild-type and polyglutamine (polyQ) transgenic strains as well as *daf-2* and *age-1* mutants, but not a *daf-16* mutant, suggesting its life span–extending effect is dependent on the DAF-16/FOXO transcription factor, a pivotal downstream effector of IIS pathway.[13] This is intriguing because increased insulin resistance and deficiency correlate with type 2 diabetes, the major adult-onset diabetes that can also be ameliorated by the *A. membranaceus* polysaccharide. The apparent paradox here implies that herbal polysaccharides may function through balancing the IIS rate, rather than simply increasing or decreasing the IIS level, to reduce pathogenesis and promote life span.[13]

Alleviation of Neurodegeneration by Herbal Polysaccharides

Neurodegenerative diseases are a group of disorders characterized by cognitive and motive pathology, which result from progressive and selective loss of neuronal function. A number of age-related neurodegenerative diseases, such as Alzheimer disease (AD) and Huntington disease (HD), are known to be linked with impaired proteostasis.[14] A set of quality control mechanisms, including the heat shock protein family, ubiquitin-proteasome system, and autophagy-lysosome system, are used by normal cells to maintain proteostasis and reduce proteotoxicity. As aging advances and stresses accumulate, however, proteostasis may be disrupted by excessive misfolded and aggregated proteins, leading to disequilibrium of cellular homeostasis and selective injury and death of neurons (Fig. 1). For example, overproduction and aggregation of amyloid-β peptide (Aβ), the main component of amyloid deposits in the brains of AD patients, can cause AD-like symptoms in animal models.[14] Therefore, maintaining proteostasis, including prevention of protein misfolding and aggregation, as well as degradation of misfolded and aggregated proteins, may be an efficient way to reduce aggregation-associated neurotoxicity. Using the human embryonic kidney cell line T-REx293 expressing the Aβ42–enhanced green fluorescent protein (EGFP) fusion protein, the polysaccharides from *Rubia cordifolia* are found to reduce Aβ aggregates by activating proteasome activity.[15] Interestingly, trehalose, a non-reducing disaccharide, can also promote mutant huntingtin protein and α-synuclein clearance by enhancing autophagy function.[16]

Pathogenic protein aggregation is known to promote the aging process. For instance, over-expression of polyQ, the critical aggregation-prone protein in HD and other polyQ diseases, is shown to expedite organismal aging and decrease life span.[13] Moreover, a number of well-elucidated signal pathways such as IIS, MAPK, and mammalian (m) TOR are associated with both aging and proteostasis, and thus regulation of these pathways to maintain proteostasis may be beneficial to age-related proteotoxic disorders.[14] For example, astragalan not only delays the age-associated increase of polyQ aggregation and neurotoxicity but also extends the life span *per se* in *C. elegans* models, and these effects are correlated with the modulation of the IIS pathway.[13] Another example is the polysaccharide from *Nerium indicum*, which is able to protect rat cortical neurons against Aβ cytotoxicity, inhibit c-Jun N-terminal kinase-1 (JNK-1) phosphorylation, and activate the survival signaling Akt.[17]

Apart from proteotoxic stress, other stresses such as oxidation and inflammation also exacerbate aging and age-related neurodegeneration. Oxidative stress can induce malfunction of energy metabolism in mitochondria and subsequently damage mitochondrial structure and genome, leading to neuronal apoptosis.[5] Because many polysaccharides have shown anti-oxidant activities, it is conceivable that herbal polysaccharides have beneficial effects against neurodegenerative diseases. In fact, anti-oxidant polysaccharides from brown seaweeds have been shown to ameliorate Aβ- and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neuronal death and behavioral deficits in mice by increasing anti-oxidant enzyme activity and inhibiting lipid peroxidation.[18,19] Besides oxidation, neuroinflammation characterized by activation of microglia is also an important hallmark in chronic neurodegenerative diseases. Although inflammation is an active defense and recovery response, it may cause neuronal damage by overproduction of inflammatory cytokines and ROS. Interestingly, some polysaccharides, *e.g.*, those from *G. lucidum* and seaweeds, are capable of antagonizing the cytotoxicity of phlogogenic lipopolysaccharides and MPTP in rat dopaminergic neurons.[19,20]

Conclusion

Recent studies have provided clear evidence for the protective effects of herbal polysaccharides against diverse aging-related stresses. Some polysaccharides are shown to regulate multiple stresses and rebuild cellular homeostasis to delay aging and age-associated pathogenesis (Fig. 1), suggesting the potential use of herbal polysaccharides in food and pharmaceutical industries. Therefore, it will be of great interest to search for more polysaccharides with similar functions and clarify their mechanisms of action.

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Author Disclosure Statement

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Address correspondence to:
Zebo Huang
School of Biosciences and Biopharmaceutics
Guangdong Pharmaceutical University
Guangzhou 510006
China

E-mail: zebohuang@qq.com; zebohuang@gdpu.edu.cn

and

Chung Wah Ma
Research & Development Centre
Infinitus (China) Company Ltd.
Guangzhou 510665
China

E-mail: william.ma@infinitus-int.com

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