

Research on the Anti-Aging Mechanisms of *Angelica sinensis*

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Abstract

Nowadays, as the global population aging continues to expedite, anti-aging has become an important topic in biomedicine. *Angelica sinensis* (hereafter referred to as *A. sinensis*), as a traditional Chinese medicinal herb, possesses significant pharmacological value; its primary active components—*Angelica sinensis* polysaccharide (ASP), ferulic acid, and (Z)-Ligustilide—exhibit pharmacological effects such as antioxidant activity, immunomodulatory properties, and anti-aging effects. Research on the anti-aging mechanisms of *A. sinensis* has always been a hotspot in scientific research; this paper elaborates on these mechanisms from three perspectives: antioxidant effects, immune – inflammatory regulation, and cellular protection. Existing studies have demonstrated that *A. sinensis* delays the aging process through a multi-targeted mechanism involving free radical scavenging, activation of the Nrf2 pathway, regulation of the TLR4 signaling pathway, protection of telomeres, and modulation of the P53/P21 and Wnt/ β -catenin pathways. However, current research is mainly limited to preclinical experiments, and there are still problems such as inconsistent extraction and preparation processes of ASP and unclear activity, which require further in-depth research and promote clinical shifting into application..



1 The biological basis of aging

With the acceleration of the global population aging process, delaying aging and promoting healthy aging have become one of the current medical hot topics. Aging is a process of functional and organic decline and deterioration in the body, involving damage at multiple levels from molecules and cells to tissues and organs. Therefore, searching for effective targets for aging intervention has become the current direction of medical research.

At the molecular level, one of the core driving forces of aging is the accumulation of genetic and tissue damage. External physical, chemical, and biological agents constantly threaten the integrity and stability of DNA. Histone modification, DNA methylation, and chromatin remodeling, and so on, can lead to genomic instability by regulating gene expression. Meanwhile, when telomeres shorten to a critical threshold with cell division, cells will enter replicative senescence. At the cellular level, mutations caused by mtDNA replication errors accumulate over time, reducing mitochondrial energy production and thereby leading to aging. In addition, the elevated activity of senescence-associated SA- β -gal and the activation of the P53/P21 signaling pathway can induce cells to enter irreversible senescence [1].

Based on discoveries at the genetic and cellular levels, several theories have gradually been formed in current aging research. The free radical theory holds that aging is the cumulative result of oxidative damage to the body's cells and tissues [2]. Free radicals generated by the environment and internal metabolism can cause damage to cellular components, which in turn leads to impairment of human body functions and accelerates aging. Telomere theory emphasizes that telomere shortening decides the limit of cell division [3]. Deletion of the ends of chromosomes leads to a decrease in cell proliferation capacity, eventually resulting in cellular senescence

and death, while telomerase synthesizes telomeric repeat sequences at chromosome ends and extends telomere length, thereby delaying cellular senescence. Immunosenescence theory points out that as immune function weakens, the body fails to clear senescent cells and inflammatory factors, leading to a continuous increase and gradual accumulation of inflammation, which in turn causes a decline in immunity [4]. theory of Inflammaging posits that cellular senescence is closely associated with SASP, which contains strong pro-inflammatory factors, including IL-6 and IL-8. These factors induce endogenous inflammation and oxidative stress, both of which accelerate the progression of cellular senescence [5].

In recent years, research on aging has continued to deepen. Guido Kroemer and colleagues have expanded the original 12 hallmarks of aging to 14, these aging characteristics are respectively: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled autophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis, extracellular matrix changes, and psychosocial isolation [6]. This framework reveals that aging is a divisible and intervenable biological process.

In summary, aging is a complex biological process driven by the synergy of multiple factors and multiple levels.

As shown in Figure 1, oxidative stress, cellular senescence, and immune-inflammatory dysregulation form a cyclic relationship through the "oxidative – inflammatory – senescence" axis. Although the theories provide a framework for anti-aging research, the multi-level nature of aging poses challenges for single-target therapeutic strategies. In contrast, the multi-target and multi-component characteristics of traditional Chinese medicine offer potential advantages in delaying aging. *Angelica sinensis*, a

traditional herb used for nourishing blood and promoting blood circulation, exhibits antioxidant, immunomodulatory, anti-inflammatory, and anti-aging effects. Based on this foundation, this

paper will systematically elucidate the molecular mechanisms underlying the anti-aging properties of *A. sinensis*.

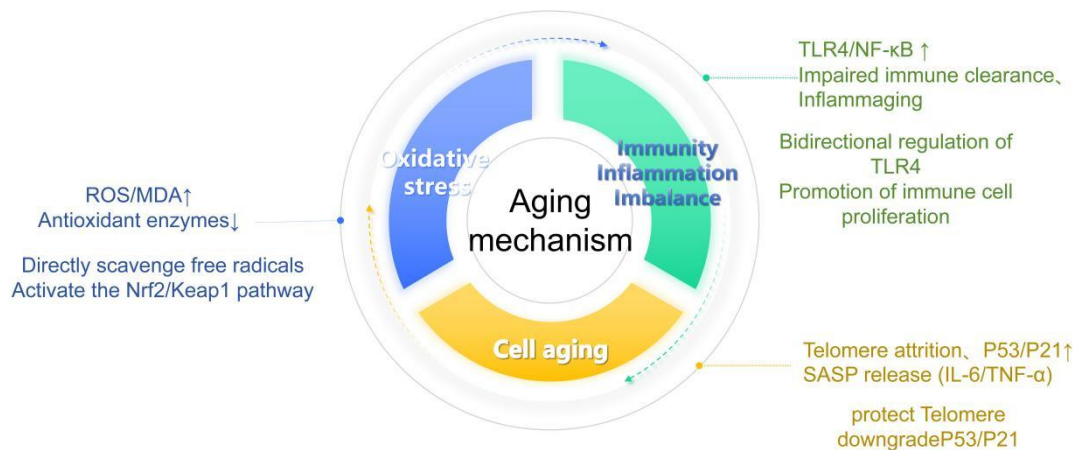


Figure 1 The "oxidation-inflammation-aging" feedback loop in the aging process. This figure illustrates the aging cycle composed of oxidative stress, cellular senescence, and immune-inflammatory dysregulation. Oxidative stress (accumulation of ROS/MDA, depletion of antioxidant enzymes) triggers telomere attrition, activates the P53/P21 pathway, and drives cells into a senescent state; senescent cells secrete SASP (represented by IL-6 and TNF- α) to amplify local inflammation, activate the TLR4/NF- κ B pathway, and promote immune-inflammatory dysregulation ; impaired immune clearance function leads to the continuous accumulation of senescent cells and oxidative damage products, which further exacerbates oxidative stress and forms a loop.

2 The anti-aging molecular basis of *Angelica sinensis*

As a traditional Chinese medicinal material, *A. sinensis* is a traditional plant that can be used both as medicine and food. It has the effects of enhancing immunity, regulating hematopoiesis, lowering blood pressure, reducing blood lipids, relieving pain, resisting inflammation, and fighting tumors, etc [7]. chemical components of *A. sinensis* are complex, which are divided into four core active components: volatile oils ((Z)-Ligustilide), organic acids (ferulic acid, etc.) polysaccharides (*A. sinensis* polysaccharide, (ASP)), and polypeptides. In addition, it also contains secondary components such as coumarins, amino acids, sterols, vitamins, and trace elements. Among them, ASP is considered the core component of the

anti-aging efficacy of *A. sinensis*.

2.1 *Angelica sinensis* polysaccharide

Angelica polysaccharide, abbreviated as ASP, is a complex polysaccharide composed of monosaccharides such as glucose, galactose, rhamnose, arabinose, and xylose. The molecular weight, molar ratio, and sugar chain structure of ASP obtained by different extraction and purification processes are not the same, so it is still impossible to unify the structural characteristics of ASP [8]. polysaccharide has a variety of pharmacologically active effects. In terms of hematopoiesis regulation, research by Liu et al. demonstrates that ASP promotes hematopoiesis by stimulating the secretion of (IL-6)

and granulocyte-macrophage colony-stimulating factor, restores hemoglobin levels to normal in hemorrhagic mice, and significantly enhances the colony-forming capacity of mouse bone marrow cells [9]. In addition to its hematopoietic effects, ASP also exhibits significant anti-inflammatory activity. Liu's article points out that ASP-4 blocks the translocation of iNOS and COX-2, as well as the phosphorylation of p65 and $I\kappa B\alpha$, thereby inhibiting the transcription of inflammatory response genes [10]. In terms of antioxidant properties, Ai using CT perfusion imaging found that rabbits administered with ASP exhibited

significantly elevated rCBF and rCBV, along with decreased rMTT and rTTP in the ischemic brain tissue, suggesting the antioxidant properties of ASP [11]. As shown in Figure 2, ASP is not a single entity but rather a functionally diverse mixture with varied structural configurations. This structural diversity not only determines its distinct pharmacological activity profiles but also provides the material basis for understanding the synergistic effects of multiple targets involved in the three major mechanisms: antioxidant protection, cellular protection, and immune regulation.

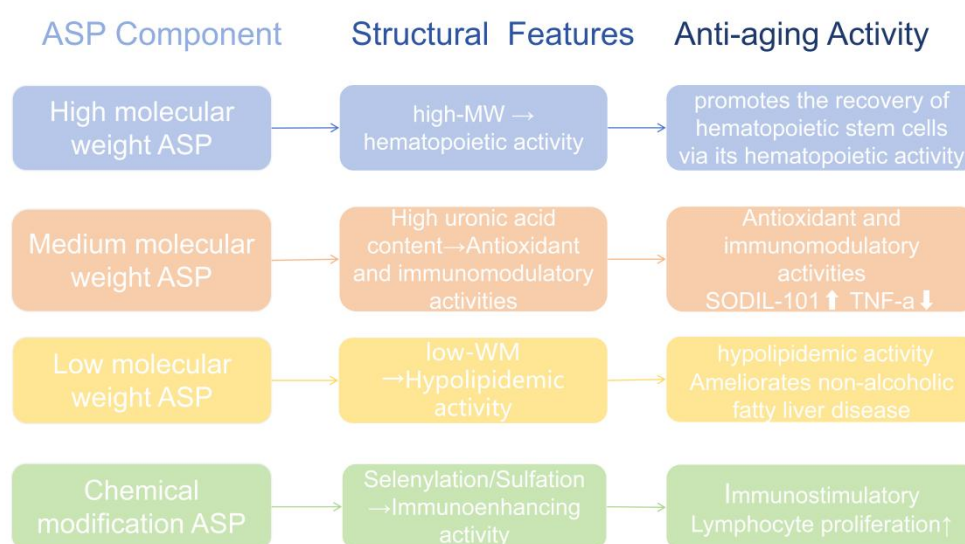


Figure 2 Corresponding relationship between different components, structural characteristics, and anti-aging activities of ASP. The structure-activity relationship of ASP is influenced by multiple dimensions: the molecular weight determines the activity direction (high molecular weight promotes hematopoiesis, medium molecular weight has both antioxidant and immune functions, low molecular weight lowers lipid); chemical modifications (selenylation, sulfation) can significantly enhance the immunomodulatory activity.

2.2 Other ingredients

Angelica polypeptide has the characteristics of easily available raw materials, low cost, rich nutrition, and high safety. At present, there are few studies on polypeptide components, but the antioxidant activity of *A. sinensis* polypeptides cannot be ignored. *A. sinensis* polypeptide extract and its active peptide fragments have good free radical scavenging activity, and their mechanism of action is the same as that of

free amino acids. Studies by Ouyang Xiaojian et al. further show that *A. sinensis* polypeptides can inhibit erastin-induced ferroptosis in HT22 hippocampal neuronal cells via Nrf2 [12]. Ferulic acid and (Z)-ligustilide are important small-molecule active ingredients in *A. sinensis*. Ferulic acid belongs to organic acids. It is one of the main index components for the quality control of *A. sinensis* stipulated in the *Chinese Pharmacopoeia*, has strong antioxidant

activity, and is closely associated with the "blood tonifying, anti-inflammatory" effects of *A. sinensis*. (Z)-Ligustilide belongs to volatile oils. It is the most characteristic and biologically active component in the volatile oil of *A. sinensis*, has a unique benzofuranone structure, and is recognized as the key material basis for the "promoting blood circulation, relieving spasm" effects of *A. sinensis* [7]. Study by Xie Xu et al. found that at a dose of 5 mg/kg, (Z)-ligustilide can significantly ameliorate ADM (doxorubicin)-induced body weight loss and limb grip strength reduction in mice, and reverse thymic injury. (Z)-Ligustilide improves thymic immune function by inhibiting the binding of T β 15 to G-actin and enhancing the microfilament assembly capacity in TECs [13]. This discovery expands the evidence for the anti-aging effect of *A. sinensis* from the antioxidant level to the level of reversing immune organ senescence, and also provides direct experimental evidence for (Z)-ligustilide as a key component of *A. sinensis* in resisting immune senescence.

3 Anti-aging Mechanism of *Angelica sinensis*

Based on the free radical theory, the Immunosenescence and Inflammaging theories, and the Telomere theory introduced in Chapter 1, combined with the current state of research on the anti-aging properties of *A. sinensis*, this chapter systematically elucidates its anti-aging mechanisms across three levels: antioxidant effects, cytoprotection, and immunomodulatory and anti-inflammatory regulation. Importantly, these dimensions are not mutually exclusive but are coupled through the "oxidation-inflammation-aging" axis, reflecting their intrinsic interplay.

3.1 Anti-oxygenation

The free radical theory holds that oxidative damage caused by the accumulation of reactive oxygen species (ROS) is the initiating factor of aging. Therefore, scavenging free radicals and performing redox

regulation are important strategies for delaying aging. Existing studies have shown that ASP exerts an antioxidant effect by directly scavenging free radicals and activating the Nrf2 signaling pathway.

3.1.1 Directly scavenge free radicals

At the cellular level, Zhuang et al. used human osteoarthritis chondrocytes induced by IL-1 β as a model, took MDA (malondialdehyde, the end product of lipid peroxidation), SOD, and CAT (catalase, endogenous antioxidant enzymes) as detection indicators, and found that ASP pretreatment could significantly reduce the level of MDA, while increasing the activities of SOD and CAT. This indicates that ASP can directly ease oxidative damage and enhance the immediate antioxidant capacity of cells [14,15]. In the organizational level, Wang Lan et al. further proved this in a D-gal-induced aging model. After ASP injection, the MDA content in the hippocampus of rats significantly decreased, SOD activity increased, and the consumption of glutathione (GSH) was reduced, indicating that ASP can not only directly scavenge free radicals, but also reduce the consumption of endogenous antioxidant substances [16]. The direct antioxidant effect of ASP has been demonstrated across all levels, from the cellular to the tissue level.

3.1.2 Activate the Nrf2/Keap1 signaling pathway

The Nrf2/Keap1 signaling pathway is the core pathway that regulates the expression of endogenous antioxidant enzymes. In normal physiological conditions, the Nrf2/Keap1 signaling pathway is in an inhibited state. When stimulated by active components, Nrf2 dissociates and translocates into the nucleus, initiating the transcription of antioxidant genes, thereby enhancing the cells' own antioxidant capacity. *A. sinensis* regulates the Nrf2/Keap1 signaling pathway and ameliorates body senescence through antioxidant effects. The activation of this pathway by *A. sinensis* has been verified in multiple models. Studies by Dongli Li have shown that Danggui

Buxue Decoction can activate the expression of antioxidant molecules such as Nrf2 and HO-1 through the Keap1-Nrf2 signaling pathway, reduce the oxidative stress level of CIH cells, and inhibit endothelial cell apoptosis, thereby ameliorating vascular endothelial cell senescence induced by intermittent hypoxia [17]. Lu et al. further discovered that fermented *A. sinensis* has a more significant effect on activating the Nrf2 pathway. It can not only enhance the expression of Nrf2, HO-1, and NQO1, but also increase the activity of antioxidant enzymes such as SOD and CAT in the liver [18]. This result indicates that appropriate processing or fermentation processes may enhance the antioxidant activity of *A. sinensis*, and also provides a direction for the optimization of extraction processes. However, most current evidence regarding the activation of the Nrf2 pathway by *A. sinensis* comes from cellular or chemically induced models; how *A. sinensis* polysaccharides interact with inflammatory signaling pathways—such as NF- κ B—under physiological aging conditions remains to be investigated.

3.2 Cytoprotection

Cellular senescence is the result of cumulative molecular damage. Once cells enter senescence, they not only lose their normal functions but also spread damage to surrounding tissues through the SASP. ASP regulates cellular senescence at multiple levels, encompassing the telomere system, mitochondria and ER, and signaling pathways. This multi-node coverage, spanning from the nucleus to the cytoplasm, confers broad-spectrum cytoprotective effects on ASP.

3.2.1 Telomere System

Telomeres shorten as cells divide; when their length reaches a critical threshold, the cells enter replicative senescence. ASP can delay telomere attrition by maintaining telomerase activity. In the X-ray-induced hematopoietic stem cell senescence model, ASP can significantly inhibit the increases in the positive rate of

SA- β -Gal staining and the proportion of G1 phase in senescent HSCs, while downregulating P53 expression and increasing telomere length and telomerase activity. This indicates that ASP has the potential to delay replicative senescence at the hematopoietic stem cell level [19]. Furthermore, it was discovered that ASP can induce senescence in human bone marrow CD34+CD38-LSCs in vitro by regulating the cellular telomere system [20]. This suggests that ASP may have differential regulatory effects on both malignant proliferative cells and normally aging cells. This differential effect is likely attributed to the structural heterogeneity of ASP preparations. ASP is a complex mixture of polysaccharides with varying molecular weights, monosaccharide compositions, and chemical modifications. However, direct comparative studies are still lacking, and this hypothesis requires further investigation.

3.2.2 Mitochondria and the endoplasmic reticulum

Besides the telomere system, ASP also protects cells by maintaining the stability of mitochondria and the endoplasmic reticulum. Based on bone marrow cell network pharmacology and RNA-seq analysis, Jiang et al. found that ASP effectively alleviated endoplasmic reticulum and mitochondrial swelling, reduced the expression of molecules involved in the endoplasmic reticulum stress response, and prevented apoptosis in bone marrow cells [21]. This discovery extends the cytoprotective mechanism of ASP from the nucleus to the cytoplasm.

3.2.3 Signaling pathway

The regulation of cell senescence by *A. sinensis* involves multiple pathways. The P53/P21 pathway is one of the executive pathways for cellular senescence. Factors such as DNA damage activate P53, which in turn upregulates P21, arresting the cell cycle at the G1 phase. ASP inhibits cells from entering the senescent state by reducing the expression of P53 protein and decreasing the regulation of P21 [19]. The Wnt/ β

-catenin pathway plays a key role in the self-renewal and differentiation of stem cells. ASP protects stromal cells from 5-FU-induced proliferation inhibition and apoptosis by activating the Wnt/ β -catenin signaling pathway [22]. However, current research on the regulation of the Wnt/ β -catenin pathway is mainly focused on stem cells and tumor cell lines, and its specific contribution and cell type dependence in normal aging tissues still remain to be further verified.

3.3 Immune - anti-inflammatory regulation

Immunosenescence and inflamm-aging are important features of aging. A decline in immune system function leads to the inability to effectively clear senescent cells, while pro-inflammatory factors continuously secreted by senescent cells further exacerbate tissue damage. The two are reciprocal causative factors and have a certain correlation. The root cause of Immunosenescence lies in the functional degeneration of the thymus. The microenvironment composed of thymic epithelial cells (TECs) directly determines the development and output efficiency of T cells, so the functional state of TECs is one of the key determinants of Immunosenescence. Recent studies have found that Thymosin β 4 can regulate the differentiation process of thymocytes by regulating cytoskeletal rearrangement and mitochondrial transfer in TECs [23], which provides a theoretical basis for understanding how the active components of *A. sinensis* delay thymic Immunosenescence by protecting TECs function. The intervention of *A. sinensis* in two aging modes is manifested as enhancing immune function and inhibiting excessive inflammation.

3.3.1 Enhance immune function

At the immune organ level, *A. sinensis* can promote the proliferation of immune organs such as the spleen and thymus. Xu Xie et al. found that in a mouse model of acute thymic degeneration induced by short-term rapamycin, administration of *A. sinensis* significantly

promoted cell proliferation in the thymic cortical region, reversed thymic atrophy, and accelerated the recovery of thymic structure [24]. This finding extends the immunopotentiating effect of *A. sinensis* from peripheral immune organs to central immune organs, providing more complete evidence at the organ level for understanding the mechanism of *A. sinensis* against immune senescence. At the immune cell level, it further activates immune function and promotes the proliferation of T cells, B cells, macrophages, and natural killer cells, and promotes the production of cytokines such as TNF- α , thereby regulating the immune system [8]. This "cell-organ" multi-layer activation mode constitutes the basic framework for *A. sinensis* to enhance immunity. Notably, a recent study also explored the potential of ASP as a vaccine adjuvant, suggesting its broader immunomodulatory capacity; however, this aspect is beyond the scope of the present review, which focuses on immunosenescence [25].

3.3.2 Inhibit excessive inflammation

ASP's regulation of the inflammatory response has been confirmed both at the cellular and animal levels. At the cellular level, Xie et al. used LPS-injured PC12 cells as a model and found that ASP can exert dual anti-apoptotic and anti-inflammatory effects by downregulating COX-1 and activating the PI3K/AKT signaling pathway, which can alleviate spinal cord injury [26]. At the animal experiment level, Cheng used D-gal to construct aging models of brain tissue and NSCs in Nestin-GFP transgenic mice. Injecting angelica polysaccharide could delay the aging of mice, and non-stem cells were isolated in vitro. It was confirmed that ASP intervention could reduce the content of MDA and decrease the release of pro-inflammatory factors such as IL-1 β , IL-6, and TNF- α , thereby delaying the process of brain aging [27]. However, the main driver of aging-related chronic inflammation (inflammaging) isn't external LPS, but

the senescence-associated secretory phenotype (SASP) that aging cells keep releasing. In the D-galactose model mentioned earlier, the observed decrease in pro-inflammatory factors suggests that ASP might intervene in inflammaging by suppressing the release of SASP components [5].

3.3.3 Signaling pathway

The TLR4 pathway is a key node linking immune activation and inflammatory responses. He Yuancong et al. completely revealed the signaling chain of the ASP-activated TLR4 pathway: ASP → TLR4 → MyD88 → TRAF6 → NF-κB. The activation of this pathway can induce the differentiation and maturation of macrophage RAW264.7, promote the expression of costimulatory molecules such as CD80/CD86/MHCII, and produce cytokines including IL-6, TNF-α, and IL-1β [28]. This pathway provides a clear framework for understanding the immune activation of ASP. Notably, different structures of ASPs may exhibit a bidirectional regulatory effect of either promotion or inhibition on the TLR4 pathway. It is closely related to the molecular weight, monosaccharide composition, and chemical modifications of ASP. Current literature has demonstrated that crude ASP extract and its various fractionated components can exert immunomodulatory effects through TLR4 [29]. Furthermore, chemical modification can significantly alter the immunological activity of ASP — studies have shown that sulfated *Angelica sinensis* polysaccharide (APS-1) can inhibit viral replication and enhance the body's immune function [30]. However, no previous study has directly compared the differential regulation of the TLR4 signaling pathway by *Angelica sinensis* polysaccharide components with varying molecular weights or chemical modifications; this represents an important direction for future structure–activity relationship studies.

3.4 Antioxidation, Immunity, and Cellular Senescence

The anti-aging mechanisms of *A. sinensis* can be

summarized into three levels. At the molecular level, *A. sinensis* directly clears ROS and MDA and activates the Nrf2/Keap1 pathway to upregulate the expression of endogenous antioxidant enzymes and reduce oxidative damage. At the cellular level, *A. sinensis* delays cellular senescence or entry into the apoptotic state by protecting telomeres, downregulating P53/P21, and regulating the Wnt/β-catenin pathway. At the system level, *A. sinensis* mitigates inflammatory aging and immune senescence by regulating pro-inflammatory and anti-inflammatory factors, as well as modulating immune cells through the TLR4 pathway. These three biological levels are not independent but are interconnected through the "oxidation–inflammation–aging" axis: oxidative stress directly triggers cellular senescence; senescent cells exacerbate inflammation via the SASP; and this inflammation further impairs immune function, leading to impaired clearance of senescent cells [31]. As a multi-target agent, *A. sinensis* simultaneously acts on three critical nodes: antioxidative inhibition of initiating factors, cellular protection disruption of execution pathways, and immune–anti-inflammatory blockade amplification of signaling pathways. So it can disrupt the positive feedback loop and render it unsustainable.

3.5 Pharmacokinetics and Safety Considerations

Although pharmacological evidence of the anti-aging effects of ASP is increasingly abundant, its pharmacokinetic properties are still severely understudied. Current limited studies on the oral absorption of ASP indicate that ASP can be absorbed into the blood circulation through endocytosis via macropinocytosis pathways as well as clathrin- and caveolin-related pathways [32]. Regarding safety, existing studies indicate that *A. sinensis*, when used as a substance with dual medicinal and food applications, exhibits a relatively high safety profile; however, *Angelica sinensis* fluid extract, volatile oils, and

polysaccharide complexes may still induce toxic reactions at certain doses and over specific time periods; therefore, the dosage and administration duration require rigorous evaluation [33].

4 Conclusion

In conclusion, *Angelica sinensis* (particularly ASP) exhibits anti-aging effects across multiple mechanisms. As the primary active component of *A. sinensis*, its polysaccharides exert anti-aging actions through various pathways—including scavenging free radicals and mitigating oxidative damage, inhibiting apoptosis, enhancing immune function, exerting anti-inflammatory effects, and regulating the telomere system. These mechanisms are not isolated but rather interrelated, collectively forming a multi-targeted aging-delaying action network for ASP. Compared to single-target drugs, the multi-targeted nature of ASP better aligns with the fundamental mechanisms underlying aging, providing a theoretical foundation for exploring and developing multi-targeted anti-aging formulations derived from *A. sinensis* as the raw material.

However, although there have been a large number of studies on the anti-aging effect of *A. sinensis* at present, there are still defects. 1. The structure-activity relationship of ASP has not been elucidated. ASP is a polysaccharide mixture with different molecular weights and different monosaccharide compositions. Most studies have not clarified the specific purification process of ASP. Modifications such as selenylation and sulfation will also significantly change the immunological activity of ASP, and the differences in anti-aging activity between ASPs with different structures have not been systematically studied. 2. Although compound preparations containing *Angelica sinensis* are currently available, the synergistic interactions among the multiple herbs in these formulas make it difficult to delineate the independent contribution of *A. sinensis*

as a single agent. 3. The gap in clinical trials. Current research on the anti-aging effects of *A. sinensis* is still at the theoretical stage, lacking rigorous clinical trials. Pharmacokinetic and toxicological data on ASP, such as oral bioavailability, in vivo metabolism, and long-term safety, are also severely lacking.

Future research should make breakthroughs in the following directions: 1. Structure-activity relationship analysis. Systematically compare the differences in anti-aging activity of ASP components with different molecular weights and different chemical modifications (selenylation, sulfation, etc.), and identify the structural type with the optimal activity. 2. Expansion of animal models. Systematically verify the life-extending effect of ASP and the improvement effect of healthspan in multiple model organisms, and fill the evidence gap between the D-gal acute aging model and physiological aging. 3. Advancement of clinical translation. After completing sufficient safety evaluations, gradually advance clinical trials.

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Conflicts of Interest

Jianli Gao is the editor-in-chief of the JECACM. The authors declare that there is no other conflict of interests.

Author Contributions

J.T. wrote the main manuscript text and prepared the figures and tables. J.G. conceptualized and supervised the project and revised the manuscript. All authors reviewed and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Availability of Data and Materials

All source data for this work (or generated in this study) are available upon reasonable request.

Supplementary Material

Not applicable.

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