

Spleen and Aging: Potential Mechanisms and Applications of Traditional Chinese Medicine Interventions

Haojie Tang^{1,2,a}, Hanjie Jin^{1,2,b}, Chaoyue Zhao^{1,2,c}, Xuting Zhu^{1,2,d},
Yaowen Zhang^{1,e}, Zhikun Bai^{1,3,f,*}

¹School of Basic Medical Sciences, Youjiang Medical University for Nationalities, Baise, China

²Graduate School, Youjiang Medical University for Nationalities, Baise, China

³Guangxi Database Construction and Application Engineering Research Center for Intracorporal Pharmacochimistry of TCM, Youjiang Medical University for Nationalities, Baise, China

^a1017574040@qq.com, ^b841327471@qq.com, ^c136374466@qq.com, ^d3358462191@qq.com,

^e841327471@qq.com, ^fbai.zhikun@ymun.edu.cn

*Corresponding author

Abstract: With the increasing global population aging, research into age-related diseases has become increasingly important. In Traditional Chinese Medicine (TCM), the spleen is regarded as the "foundation of postnatal life," playing a crucial role in the generation of Qi and blood, as well as in digestion and absorption. This review explores the role of the spleen in the aging process and examines the potential mechanisms through which TCM can regulate spleen function and delay aging. By analyzing relevant literature, this article aims to provide theoretical support for the application of TCM in geriatric medicine.

Keywords: Spleen; Aging; Traditional Chinese Medicine; Qi and Blood; Geriatric Medicine

1. Introduction

Aging is a complex biological process characterized by a gradual decline in physiological functions, increased susceptibility to diseases, and ultimately, death. It is influenced by a multitude of genetic, environmental, and lifestyle factors. The mechanisms underlying aging involve a series of biological changes at the molecular, cellular, and systemic levels, which contribute to the functional decline associated with aging. These include oxidative stress, telomere shortening, mitochondrial dysfunction, and inflammation, all of which play significant roles in the aging process and the onset of age-related diseases^[1,2].

In Traditional Chinese Medicine (TCM), the spleen is considered a vital organ responsible for the production and regulation of Qi (vital energy), blood, and bodily fluids. It is essential for digestion and nutrient absorption, which are crucial for maintaining overall health and vitality. TCM posits that a well-functioning spleen can enhance the body's resistance to diseases and promote longevity. The spleen's health is intricately linked to the prevention of aging and age-related disorders, as it influences the body's ability to nourish and support other organs^[3,4].

The role of TCM in the prevention and treatment of aging is increasingly recognized in modern research. TCM employs a holistic approach, focusing not only on symptoms but also on the underlying imbalances within the body. Various herbal formulations and therapies are used to rejuvenate the spleen and enhance overall health, thereby mitigating the effects of aging. This integrative approach has shown promise in improving health outcomes and enhancing the quality of life in older adults, making TCM a valuable resource in the quest for longevity and healthy aging^[5,6].

In summary, understanding the definitions and mechanisms of aging, alongside the importance of the spleen in TCM, provides a foundation for exploring the role of traditional medicine in aging prevention and treatment. As the global population ages, the integration of TCM principles and practices in modern healthcare could offer novel strategies for promoting longevity and enhancing the quality of life among older adults.

2. Spleen and Aging

2.1 The Relationship Between Spleen Physiological Functions and Aging

2.1.1 The Role of the Spleen in Qi and Blood Generation

The spleen plays a pivotal role in the generation of Qi (vital energy) and blood, which are essential for maintaining overall health and vitality. In traditional Chinese medicine, the spleen is viewed as the organ responsible for the transformation and transportation of nutrients derived from food into Qi and blood. This process is crucial, especially during aging when the body's ability to assimilate nutrients may decline. Research indicates that the spleen's ability to produce blood cells diminishes with age, leading to anemia and other hematological disorders. Moreover, the spleen's contribution to hematopoiesis is significant, as it serves as a site for extramedullary hematopoiesis during stress or disease states, particularly in the elderly, who often experience a compensatory increase in splenic blood cell production to counteract bone marrow insufficiency^[7,8]. Additionally, the spleen's red pulp is involved in the clearance of senescent erythrocytes, thus maintaining a healthy red blood cell population, which is crucial for oxygen transport and overall energy levels in the body^[9].

2.1.2 The Impact of the Spleen on Digestion and Absorption

The spleen's influence extends to the digestive system, where it plays a critical role in nutrient absorption and metabolism. As a part of the reticuloendothelial system, the spleen filters blood and removes old or damaged red blood cells, which is vital for maintaining a healthy circulatory system. In the context of aging, the spleen's efficiency in processing nutrients and supporting digestive health may decline, leading to malabsorption issues and nutritional deficiencies. Studies have shown that the aging spleen exhibits alterations in its microenvironment, which can affect the proliferation and function of splenic macrophages and other immune cells involved in digestion^[7,10]. Furthermore, the spleen's interaction with the gut through the gut-spleen axis highlights its role in modulating digestive processes and immune responses, thereby affecting overall health and well-being in aged individuals^[11].

2.1.3 The Connection Between the Spleen and the Immune System

The spleen is a critical organ in the immune system, acting as a reservoir for immune cells and a site for the initiation of immune responses against blood-borne pathogens. As individuals age, the immune function of the spleen often declines, leading to increased susceptibility to infections and reduced vaccine efficacy. This phenomenon, known as immunosenescence, is characterized by a decrease in the production and function of T and B lymphocytes within the spleen^[10,12]. Additionally, the aging spleen exhibits changes in its architecture, including a reduction in the number of germinal centers and alterations in the splenic microenvironment that affect lymphocyte maturation and proliferation^[7,13]. The interaction between the spleen and the nervous system further complicates this relationship, as neuroimmune communication can influence splenic immune responses and overall systemic immunity, particularly in the context of chronic inflammation associated with aging^[11]. Thus, the spleen's role in the immune system is multifaceted, and its decline in function with age poses significant implications for health and longevity.

2.2 The Impact of Aging on Spleen Function

2.2.1 Age-Related Decline in Spleen Function

Aging significantly affects the immune system, with the spleen undergoing notable structural and functional changes. One of the most prominent alterations is the architectural disorganization of the splenic white pulp, which is essential for the immune response. Research indicates that aged spleens exhibit a reduction in T cell zone reticular cells (TRCs), which are crucial for maintaining the organization of splenic architecture. This decline correlates with diminished concentrations of chemokines such as CCL19 and CCL21, leading to impaired T cell homing and overall immune dysfunction. The loss of TRCs and the subsequent blending of T and B cell zones further contribute to the compromised immune responses observed in older individuals, highlighting the spleen's critical role in age-related immunosenescence^[14,15].

2.2.2 The Relationship Between Age-Related Diseases and Spleen Function

Aging is associated with an increased prevalence of various diseases, many of which are linked to splenic dysfunction. For instance, in conditions like sickle cell anemia, splenic function deteriorates early in life, leading to complications such as autosplenectomy and splenomegaly. These changes are

attributed to the mechanical stress on the spleen from abnormal red blood cell shapes, which can cause splenic sequestration and functional decline. Studies have shown that the spleen's ability to filter abnormal cells is significantly impaired in aging populations, which exacerbates the risk of infections and other age-related diseases. Moreover, the interplay between aging and chronic inflammatory states can further compromise splenic function, leading to a vicious cycle of immune dysregulation and heightened disease susceptibility^[16,17].

2.2.3 Manifestations and Mechanisms of Spleen Deficiency Symptoms

Spleen deficiency, as recognized in traditional Chinese medicine, manifests through various symptoms including fatigue, poor digestion, and a compromised immune response. The underlying mechanisms often involve disruptions in metabolic pathways, oxidative stress, and alterations in cytokine profiles. For instance, aging leads to increased levels of pro-inflammatory cytokines and a decrease in anti-inflammatory mediators, resulting in a systemic inflammatory state that affects spleen function. Furthermore, conditions such as oxidative stress and nutrient deficiencies can impair the spleen's ability to regulate immune responses effectively. Research has shown that interventions aimed at restoring balance in these pathways can mitigate the symptoms of spleen deficiency, underscoring the importance of understanding the biological mechanisms at play^[18,19].

2.3 The Regulatory Role of Traditional Chinese Medicine on the Spleen

2.3.1 Commonly Used Traditional Chinese Medicines and Their Effects on the Spleen

Traditional Chinese Medicine (TCM) has long recognized the spleen's critical role in digestion and nutrient absorption. Common herbs such as Ginseng (Ren Shen), Atractylodes (Bai Zhu), and Poria (Fu Ling) are frequently used to tonify the spleen and enhance its function. Ginseng is known for its qi-invigorating properties, which help in bolstering the spleen's energy, while Atractylodes is effective in resolving dampness and promoting digestion. Poria, with its diuretic properties, also aids in strengthening the spleen by eliminating excess moisture that can lead to digestive issues. Studies have shown that these herbs can improve gastrointestinal motility and enhance nutrient absorption, thereby supporting overall health and vitality^[3,20]. Furthermore, the combination of these herbs in formulations like Si Jun Zi Tang has demonstrated efficacy in treating spleen deficiency syndromes, which are characterized by symptoms such as fatigue, poor appetite, and bloating^[21].

2.3.2 Methods of Spleen Nourishment in Traditional Chinese Theory

In TCM, the spleen is often referred to as the "source of postnatal qi," emphasizing its importance in energy production and overall health. Various methods are employed to nourish the spleen, including dietary recommendations and specific herbal formulas. TCM practitioners advocate for warm, cooked foods that are easy to digest, such as congee and soups, which help to strengthen spleen function. Additionally, herbal treatments such as Huang Qi (Astragalus) and Bai Zhu (Atractylodes) are frequently prescribed to tonify the spleen and enhance its qi. Techniques like acupuncture and moxibustion are also utilized to stimulate spleen points, promoting better energy flow and digestive health^[3,22]. Recent studies have highlighted the significance of these approaches in managing conditions like gastroparesis, where spleen and stomach qi deficiency is a common underlying issue^[3].

2.3.3 Application of Herbal Formulas in Aging Interventions

The application of traditional Chinese herbal formulas in aging interventions has gained attention as a potential strategy for promoting longevity and enhancing quality of life. Formulas such as Si Jun Zi Tang and Jiangu Granule have been studied for their effects on age-related conditions, particularly in modulating gut microbiota and improving immune function. Research indicates that these formulas can positively influence the gut-brain axis, which is crucial for cognitive health in aging populations. For instance, Si Jun Zi Tang has shown promise in improving cognitive deficits in mouse models by regulating gut microbiota diversity and enhancing synaptic health^[21,23]. Similarly, Jiangu Granule has been linked to improved bone health in postmenopausal women, suggesting that TCM can address multiple aspects of aging through comprehensive approaches that include dietary, herbal, and lifestyle modifications^[24,25]. These findings underscore the potential of TCM in developing holistic strategies for aging interventions, focusing on the spleen's regulatory role in maintaining health and vitality throughout the aging process.

2.4 Modern Research Supporting the Regulation of the Spleen by Traditional Chinese Medicine

2.4.1 Clinical Research on Traditional Chinese Medicine Interventions for Aging

Recent studies have increasingly highlighted the efficacy of Traditional Chinese Medicine (TCM) in addressing age-related health issues, particularly through its impact on the spleen, which is believed to play a crucial role in the aging process. Research indicates that TCM interventions can significantly improve cognitive function and overall well-being in elderly patients. For instance, a clinical trial involving herbal formulas targeting spleen deficiency showed promising results in enhancing sleep quality and modulating gut microbiota, which is vital for maintaining health in older adults^[26]. Additionally, TCM approaches, such as the use of *Pseudostellaria heterophylla* and Shenling Baizhu Powder, have demonstrated their ability to alleviate symptoms associated with spleen deficiency, including fatigue and digestive issues, thereby improving the quality of life for elderly individuals^[27,28]. These findings underscore the potential of TCM not only to treat the symptoms of aging but also to address underlying deficiencies that exacerbate age-related decline, thus offering a holistic approach to geriatric care.

2.4.2 Exploration of Mechanisms of Traditional Chinese Medicine from a Modern Medical Perspective

The mechanisms underlying the effects of TCM on the spleen and aging have garnered significant interest from modern medical research. Studies reveal that TCM operates through a multi-target and multi-component approach, which contrasts with the single-target focus typical of Western medicine. For example, the modulation of gut microbiota is a key pathway through which TCM exerts its effects, as evidenced by research demonstrating how TCM can enhance the diversity and function of gut bacteria, which is crucial for immune regulation and metabolic health^[29]. Furthermore, the immunomodulatory properties of various TCM herbs, such as *Codonopsis Radix*, have been shown to support spleen function and overall vitality by enhancing immune response and promoting nutrient absorption^[30]. This complex interplay between TCM and modern scientific understanding highlights the importance of integrating traditional practices with contemporary research to elucidate the biological underpinnings of TCM therapies.

2.4.3 Integration of Traditional Chinese Medicine with Modern Treatment Approaches

The integration of TCM with modern medical practices presents a promising avenue for enhancing treatment outcomes, particularly for conditions related to spleen dysfunction and aging. Recent studies advocate for a complementary approach, where TCM is used alongside conventional therapies to maximize efficacy and minimize side effects. For instance, the combination of TCM formulas with Western pharmacological agents has been shown to improve therapeutic effects in managing chronic conditions such as diabetes and cancer^[31,32]. Additionally, the use of artificial intelligence and data mining techniques in TCM research is paving the way for personalized medicine, allowing for tailored treatment regimens that consider individual patient profiles and the specificities of TCM syndromes^[33]. This synergistic approach not only enhances the therapeutic potential of TCM but also promotes a more nuanced understanding of disease management that respects both traditional wisdom and modern scientific rigor.

2.5 The Relationship Between the Spleen, Aging, and Lifestyle

2.5.1 The Impact of Dietary Habits on Spleen Health

Dietary habits play a crucial role in the health of the spleen, particularly as individuals age. Research indicates that unhealthy eating patterns, such as high-fat diets, can induce significant alterations in spleen architecture and immune function. For instance, a study demonstrated that a high-fat diet led to increased recruitment of lymphocytes, sinusoidal dilatations, and necrotic changes in the spleen, indicating immune system activation and potential dysfunction associated with obesity and metabolic syndrome^[34]. Furthermore, specific dietary practices, such as fast eating and late-night snacking, have been correlated with increased intra-pancreatic fat deposition, which may also adversely affect spleen function^[35]. The consumption of two meals per day has been associated with greater intrapancreatic fat deposition compared to three meals, suggesting that meal frequency can influence not just metabolic health but also the health of the spleen^[36]. Overall, maintaining a balanced diet rich in nutrients is essential for preserving spleen health and mitigating age-related decline in immune function.

2.5.2 The Relationship Between Exercise and Spleen Function

Physical activity is well-documented to enhance immune function and overall health, including the health of the spleen. Exercise has been shown to influence the accumulation and functionality of immune cells, including myeloid-derived suppressor cells (MDSCs), which are pivotal in the immune response^[37]. A study involving mice demonstrated that voluntary wheel running significantly reduced the levels of immature myeloid cells in the spleen, suggesting that regular physical activity may delay the accumulation of immunosuppressive cells, thereby promoting a more robust immune response^[37]. Moreover, exercise has been associated with improved lymphocyte composition and functionality in lymphoid tissues, including the spleen, which is crucial for effective immune responses^[38]. Interestingly, aerobic exercise training has been linked to reduced inflammation and enhanced immune cell circulation, further supporting the notion that regular physical activity is beneficial for spleen health and immune function, especially in aging populations^[39].

2.5.3 The Influence of Psychological Factors on Aging and the Spleen

Psychological factors, including stress and mental well-being, significantly impact the aging process and the function of the spleen. Chronic psychological stress has been shown to exacerbate inflammation and compromise immune function, which can be particularly detrimental as individuals age^[40]. The spleen serves as a reservoir for inflammatory myeloid cells, which can be mobilized during acute stress, leading to systemic inflammation and potential cognitive deficits^[41]. Furthermore, studies indicate that mindfulness and positive psychological factors can mitigate the effects of stress on health, enhancing resilience and promoting better immune responses^[42]. For instance, individuals with higher mindfulness dispositions demonstrated lower psychological distress during stressful events, suggesting that psychological well-being is crucial for maintaining immune health, including spleen function^[42]. Thus, fostering mental well-being through psychological interventions may be an effective strategy to support spleen health and counteract the negative impacts of aging.

3. Conclusion

The spleen plays a pivotal role in the aging process, serving as a critical organ in maintaining immune function, hematopoiesis, and overall homeostasis. As individuals age, the functional capacity of the spleen gradually declines, leading to a compromised immune response and increased susceptibility to various diseases. This decline is not merely a physiological occurrence; it has profound implications for the health span of aging populations.

Traditional Chinese Medicine (TCM) offers a unique perspective on the regulation of spleen function, emphasizing the importance of a balanced lifestyle and the use of herbal remedies. TCM posits that the spleen is fundamental to the production of Qi (vital energy) and blood, which are essential for sustaining bodily functions and combating the effects of aging. Recent studies have indicated that specific TCM formulations may enhance spleen health, thereby potentially mitigating some aging-related decline. The synergistic effects of these natural compounds could revolutionize approaches to age-related disorders, suggesting that TCM provides a complementary strategy alongside conventional medicine.

However, it is essential to balance the diverse findings in this area of research. While some studies support the efficacy of TCM in enhancing spleen function and delaying aging, others highlight the need for rigorous scientific validation and standardization of herbal treatments. Therefore, future research should focus on elucidating the mechanisms underlying the actions of TCM on spleen health, employing modern methodologies such as molecular biology and genomics.

Additionally, clinical applications must be informed by evidence-based practices, integrating TCM with Western medical approaches to create holistic treatment strategies. Future studies could also explore the potential of personalized medicine in TCM, tailoring interventions based on individual physiological profiles and specific aging-related challenges.

In summary, the spleen's significance in the aging process cannot be overstated. The potential of TCM in regulating spleen function and promoting longevity is an exciting frontier in gerontology. By fostering interdisciplinary collaboration and emphasizing rigorous scientific inquiry, we can unlock the therapeutic potential of TCM, paving the way for innovative solutions to enhance health in our aging populations.

Declarations

Authors Contributions

Haojie Tang and Hanjie Jin contributed to data analyses, interpretation, and drafting of the manuscript. Chaoyue Zhao, Xuting Zhu and Yaowen Zhang contributed to the acquisition of data and drafting of the manuscript. All authors made substantial contributions to critically revising the manuscript. All authors approved the final version of the manuscript.

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References

- [1] Golubev A G. *An essay on the nominal vs. real definitions of aging*[J]. *Biogerontology*, 2021, 22(4): 441-457.
- [2] Pezzoli S, Giorgio J, Martersteck A, et al. *Successful cognitive aging is associated with thicker anterior cingulate cortex and lower tau deposition compared to typical aging*[J]. *Alzheimer's & Dementia*, 2024, 20(1): 341-355.
- [3] Yu Y H, Yu Y S, Cheng X H. *Clinical effects of a traditional Chinese medicine nursing programme to intervene in gastric pain of the spleen and stomach with Qi deficiency*[J]. *World Journal of Clinical Cases*, 2023, 11(21): 5056.
- [4] Wang H, Wang Y. *What Makes the Gut-Lung Axis Working? From the Perspective of Microbiota and Traditional Chinese Medicine*[J]. *Canadian Journal of Infectious Diseases and Medical Microbiology*, 2024, 2024(1): 8640014.
- [5] Tan M, Li Q, Yang B, et al. *Insight of Chinese Herbal Medicine in Treating Osteoporosis: Achievements from 2013 to 2023*[J]. *The American Journal of Chinese Medicine*, 2024, 52(05): 1303-1328.
- [6] Ho T J, Ahmed T, Shibu M A, et al. *A prospective review of the health-promoting potential of Jing Si Herbal Tea*[J]. *Tzu Chi Medical Journal*, 2024, 36(1): 1-22.
- [7] Wei Y, Wang T, Liao L, et al. *Brain-spleen axis in health and diseases: A review and future perspective* [J]. *Brain Research Bulletin*, 2022, 182: 130-140.
- [8] Sun Z, Wang B, Shen Y, et al. *MXRA7 is involved in megakaryocyte differentiation and platelet production* [J]. *Blood Science*, 2023, 5(03): 160-169.
- [9] Klei T R L, Dalimot J, Nota B, et al. *Hemolysis in the spleen drives erythrocyte turnover*[J]. *Blood, The Journal of the American Society of Hematology*, 2020, 136(14): 1579-1589.
- [10] Alexandre Y O, Mueller S N. *Splenic stromal niches in homeostasis and immunity*[J]. *Nature Reviews Immunology*, 2023, 23(11): 705-719.
- [11] Groenen AG, Lipscomb M, Bossardi Ramos R, et al. *Resolvin D1 suppresses macrophage senescence and splenic fibrosis in aged mice*[J]. *Prostaglandins Leukot Essent Fatty Acids*. 2024, 202: 102634.
- [12] Long B, Koyfman A, Gottlieb M. *Complications in the adult asplenic patient: A review for the emergency clinician*[J]. *The American Journal of Emergency Medicine*, 2021, 44: 452-457.
- [13] Tahir F, Ahmed J, Malik F. *Post-splenectomy sepsis: a review of the literature*[J]. *Cureus*, 2020, 12(2).
- [14] Masters A R, Jellison E R, Puddington L, et al. *Attrition of T cell zone fibroblastic reticular cell number and function in aged spleens*[J]. *Immunohorizons*, 2018, 2(5): 155-163.
- [15] Huang Y, Liu Z, Li M, et al. *Deciphering the impact of aging on splenic endothelial cell heterogeneity and immunosenescence through single-cell RNA sequencing analysis*[J]. *Immunity & Ageing*, 2024, 21(1): 48.
- [16] Nardo-Marino A, Glenthøj A, Brewin J N, et al. *The significance of spleen size in children with sickle cell anemia*[J]. *American Journal of Hematology*, 2022, 97(12): 1520-1528.
- [17] El Hoss S, Cochet S, Marin M, et al. *Insights into determinants of spleen injury in sickle cell anemia*[J]. *Blood Advances*, 2019, 3(15): 2328-2336.
- [18] Ying X, Zhixiu S, Yun G, et al. *Effect of chiropractic manipulation on disrupted epithelium barrier and its mechanism of specialized pro-resolving mediators in a spleen-deficiency murine model*[J]. *Journal of Traditional Chinese Medicine*, 2019, 39(5).
- [19] Yi Y, Li Y, Guo S, et al. *Elucidation of the reinforcing spleen effect of jujube fruits based on metabolomics and intestinal flora analysis*[J]. *Frontiers in Cellular and Infection Microbiology*, 2022,

12: 847828.

[20] Xia W, Liu Q, Zhou H, et al. Study on the Spectrum-Effect Relationship of the Traditional Effect of Saponins in *Glycyrrhiza uralensis* Fisch[J]. *International Journal of Analytical Chemistry*, 2021, 2021(1): 6617033.

[21] Ke H, Zhang X, Liang S, et al. Study on the anti-skin aging effect and mechanism of Sijunzi Tang based on network pharmacology and experimental validation[J]. *Journal of Ethnopharmacology*, 2024: 118421.

[22] Guo H L, Zhao J, Feng W Y, et al. Treatment of abdominal pain due to deficiency syndrome of the spleen and stomach with Bian stone plus TCM iontophoresis: A case report[J]. *Medicine*, 2024, 103(17): e37858.

[23] Li Z, Zeng Q, Hu S, et al. Chaihu Shugan San ameliorated cognitive deficits through regulating gut microbiota in senescence-accelerated mouse prone 8[J]. *Frontiers in Pharmacology*, 2023, 14: 1181226.

[24] Sun P, Zhang C, Huang Y, et al. Jiangu granule ameliorated OVX rats bone loss by modulating gut microbiota-SCFAs-Treg/Th17 axis[J]. *Biomedicine & Pharmacotherapy*, 2022, 150: 112975.

[25] Wang Y L, Shu X H, Zhang X, et al. Effects of two polysaccharides from traditional Chinese medicines on rat immune function[J]. *Frontiers in Veterinary Science*, 2021, 8: 703956.

[26] Zeng H, Xu J, Zheng L, et al. Traditional Chinese herbal formulas modulate gut microbiome and improve insomnia in patients with distinct syndrome types: insights from an interventional clinical study [J]. *Frontiers in Cellular and Infection Microbiology*, 2024, 14: 1395267.

[27] Xiao Q, Zhao L, Jiang C, et al. Polysaccharides from *Pseudostellaria heterophylla* modulate gut microbiota and alleviate syndrome of spleen deficiency in rats[J]. *Scientific Reports*, 2022, 12(1): 20217.

[28] Qiao B, Xiao N, Deng N, et al. Shenling Baizhu powder attenuates lard diet in a fatigued state-induced diarrhea via targeting microbial metabolites short chain fatty acids-mediated lipid metabolism[J]. *3 Biotech*, 2024, 14(9): 203.

[29] Li J, Li D, Chen Y, et al. Gut microbiota and aging: traditional Chinese medicine and modern medicine[J]. *Clinical Interventions in Aging*, 2023: 963-986.

[30] Shi Q, Chen Z, Yang J, et al. Review on the biological activities of *Codonopsis Radix* Tonic[J]. *Journal of Ethnopharmacology*, 2024: 118334.

[31] Xu X, Chen Y, Zhang X, et al. Modular characteristics and the mechanism of Chinese medicine's treatment of gastric cancer: a data mining and pharmacology-based identification[J]. *Annals of Translational Medicine*, 2021, 9(24): 1777.

[32] Liao Y, Du X, Fu Y, et al. Mechanism of traditional Chinese medicine in treating overactive bladder[J]. *International Urology and Nephrology*, 2023, 55(3): 489-501.

[33] Song Z, Chen G, Chen C Y C. AI empowering traditional Chinese medicine?[J]. *Chemical Science*, 2024, 15(41): 16844-16886.

[34] Asghar A, Akhtar T, Batool T, et al. High-fat diet-induced splenic, hepatic, and skeletal muscle architecture damage: cellular and molecular players[J]. *Molecular and Cellular Biochemistry*, 2021, 476(10): 3671-3679.

[35] Niki A, Baden M Y, Kato S, et al. Consumption of two meals per day is associated with increased intrapancreatic fat deposition in patients with type 2 diabetes: a retrospective study[J]. *BMJ Open Diabetes Research and Care*, 2022, 10(5): e002926.

[36] Mizzoni D, Logozzi M, Di Raimo R, et al. Hydrogen-Rich Alkaline Water Supplementation Restores a Healthy State and Redox Balance in H₂O₂-Treated Mice[J]. *International Journal of Molecular Sciences*, 2024, 25(12): 6736.

[37] Garritson J, Krynski L, Haverbeck L, et al. Physical activity delays accumulation of immunosuppressive myeloid-derived suppressor cells[J]. *PLoS One*, 2020, 15(6): e0234548.

[38] Estruel-Amades S, Ruiz-Iglesias P, Périz M, et al. Changes in lymphocyte composition and functionality after intensive training and exhausting exercise in rats[J]. *Frontiers in Physiology*, 2019, 10: 1491.

[39] Zhang S, Zhu L, Peng Y, et al. Long-term running exercise improves cognitive function and promotes microglial glucose metabolism and morphological plasticity in the hippocampus of APP/PS1 mice[J]. *Journal of neuroinflammation*, 2022, 19(1): 34.

[40] Zhou H, Han X, Huang C, et al. Exercise-induced adaptive response of different immune organs during ageing[J]. *Ageing Research Reviews*, 2024: 102573.

[41] Xu D, Zhang Y, Xie B, et al. The spleen mediates chronic sleep restriction-mediated enhancement of LPS-induced neuroinflammation, cognitive deficits, and anxiety-like behavior[J]. *Ageing (Albany NY)*, 2020, 12(15): 15446.

[42] Conversano C, Di Giuseppe M, Miccoli M, et al. Mindfulness, age and gender as protective factors against psychological distress during COVID-19 pandemic[J]. *Frontiers in psychology*, 2020, 11: 1900.