대한융합한의학회지 제6권 제2호(2024년 12월)
J Conver Korean Med. 2024;6(2):33-39

ISSN 2799-2977, E-ISSN 2799-4066
http://dx.doi.org/10.2305/ackm.2024.6.2.33

Original Article

Heparan Sulfate in Alzheimer's Disease: Decoding Mechanisms, Exploring Therapeutics, and Integrating Traditional Korean Medicine

권빛나[1,2#], 김동욱[1,2#], 배기상[1,2,3*]

1. 원광대학교 한의과대학 약리학교실
2. 원광대학교 한방심신증후군연구센터
3. 원광대학교 한국전통의학연구소

Heparan Sulfate in Alzheimer's Disease: Decoding Mechanisms, Exploring Therapeutics, and Integrating Traditional Korean Medicine

Bitna Kweon[1,2#], Dong-Uk Kim[1,2#], Gi-Sang Bae[1,2,3*]

1: Department of Pharmacology, College of Korean Medicine, Wonkwang University
2: Hanbang Cardio-Renal Syndrome Research Center, Wonkwang University
3: Research center of Traditional Korean medicine, Wonkwang University

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that remains one of the most significant medical challenges of the 21st century, characterized by relentless cognitive decline, memory impairment, and functional loss. Despite decades of research, effective disease-modifying therapies remain elusive, leaving an urgent need for novel therapeutic strategies. Heparan sulfate (HS), a highly heterogeneous glycosaminoglycan found ubiquitously in the extracellular matrix and on cell surfaces, has emerged as a crucial player in the complex pathophysiology of AD. Its interactions with amyloid-beta (Aβ) peptides promote aggregation and plaque formation, while its binding to hyperphosphorylated tau facilitates neurofibrillary tangle formation, both of which are hallmark features of AD. Additionally, HS modulates neuroinflammatory cascades by influencing microglial activation and cytokine release, further contributing to neuronal damage and disease progression. Beyond its pathogenic roles, HS represents a promising therapeutic target, with potential strategies ranging from synthetic HS mimetics to enzyme inhibitors designed to modulate its activity. In parallel, the integration of Korean Medicines (KM), which has shown efficacy in addressing neuroinflammatory and cognitive disorders through herbal and holistic approaches, offers a unique perspective in the quest for innovative AD treatments. Herbs such as Gastrodia elata and Poria cocos exhibit neuroprotective and anti-inflammatory properties, making them potential candidates for HS-modulating therapies. This review provides a detailed exploration of the biological significance of HS in AD, evaluates emerging therapeutic approaches, and highlights the potential synergy between modern biomedical advancements and the principles of KM. By bridging the gap between traditional knowledge and cutting-edge science, this synthesis lays the groundwork for a transformative, integrative paradigm in AD treatment, aiming to address both the pathological and symptomatic aspects of the disease.

Key words : Alzheimer's Disease (AD), Heparan sulfate (HS), amyloid-beta (Aβ), neuroinflammaton, Korean medicines

#First author: Bitna Kweon, Department of Pharmacology, College of Korean Medicine, Wonkwang University
Tel: +82-63-850-6842, Email: kbn306@naver.com
Dong-Uk Kim, Department of Pharmacology, College of Korean Medicine, Wonkwang University,
Tel: +82-63-850-6842, Email: ckck202@naver.com
*Corresponding author: Gi-Sang Bae, Department of Pharmacology, College of Korean Medicine, Wonkwang University,
Tel: +82-63-850-6842, Email: baegs888@wku.ac.kr
·Received : 05 December 2024 ·Revised : 26 December 2024 ·Accepted : 27 December 2024

Introduction

Alzheimer's Disease (AD) stands as one of the most pressing challenges in modern medicine, driven by its widespread prevalence, profound societal impact, and the absence of effective disease-modifying therapies. As the global population ages, the incidence of AD continues to rise, imposing a substantial socioeconomic burden on healthcare systems, families, and caregivers[1]. The complexity of AD pathophysiology, marked by its multifactorial nature and progressive neurodegeneration, has hindered the development of curative interventions. Current pharmacological treatments primarily aim to manage symptoms, offering only temporary relief from cognitive decline without addressing the root causes of the disease[2].

Among the numerous factors implicated in AD progression, Heparan sulfate (HS), a structurally diverse glycosaminoglycan, has emerged as a critical mediator of its pathogenesis. Found ubiquitously in the extracellular matrix (ECM) and on cellular surfaces, HS participates in a wide array of biological processes, including cell signaling, molecular trafficking, and tissue repair[3]. Recent discoveries have illuminated its significant role in key pathological features of AD, such as the formation and deposition of amyloid plaques, tau protein aggregation, and the amplification of neuroinflammatory responses[4]. These processes are intricately linked to disease progression, and HS appears to function as a central molecular hub that exacerbates these pathological cascades.

Furthermore, HS's structural heterogeneity allows it to bind a variety of proteins, including amyloid-beta (A β) and tau, stabilizing their pathological conformations and facilitating their accumulation in the brain[5]. Its role extends to modulating immune responses, where HS influences microglial activation, cytokine release, and the propagation of neuroinflammation, which are increasingly recognized as pivotal contributors to neuronal damage and cognitive impairment in AD[6]. Given these diverse roles, HS has emerged as an attractive therapeutic target, with interventions aiming to modulate its activity or disrupt its pathological interactions[7].

In tandem with these advances in molecular research, the potential of Korean Medicines (KM) in addressing neuro-degenerative diseases has gained increasing recognition. KM, rooted in holistic principles and an integrative approach, emphasizes restoring balance within the body and mind. Its long history of application in managing cognitive disorders and neuroinflammation positions it as a valuable complementary avenue for AD treatment. Herbal remedies such as Gastrodia elata and Poria cocos, which exhibit neuro-protective, anti-inflammatory, and antioxidant properties, offer promising potential for modulating HS-related pathways[8,9].

This review aims to bridge these two domains-modern molecular insights into HS biology and the practices of KM-to propose a multidisciplinary strategy for AD management. By exploring the synergy between HS-targeted therapies and KM-derived interventions, we hope to lay the foundation for innovative therapeutic paradigms that address both the underlying mechanisms and symptomatic manifestations of AD. This integrative approach underscores the necessity of combining scientific advancements with traditional medical philosophies to confront the complexities of AD comprehensively.

Background: Heparan Sulfate and Its Multifaceted Roles

2.1. Structural and Functional Diversity of HS

Heparan sulfate (HS) is a highly complex glycosaminoglycan synthesized through a multistep enzymatic process involving glycosyltransferases, epimerases, and sulfotransferases[10]. This intricate biosynthetic pathway produces HS chains with significant structural heterogeneity, characterized by varying sulfation patterns, chain lengths, and disaccharide compositions[10]. Such variability is critical

ISSN 2799-2977, E-ISSN 2799-4066
http://dx.doi.org/10.2305/ackm.2024.6.2.33

for HS's ability to interact with a wide range of biomolecules, including growth factors, cytokines, and extracellular matrix (ECM) proteins[3].

HS plays pivotal roles in diverse biological processes. In cell adhesion, HS anchors cells to the ECM, facilitating tissue organization and stability[11]. Its role in signal transduction is particularly significant; HS acts as a co-receptor for numerous ligands, such as fibroblast growth factors (FGFs) and vascular endothelial growth factors (VEGFs), enhancing their receptor binding and downstream signaling[12]. Additionally, HS contributes to ECM organization by influencing the structural integrity of proteoglycan networks[4]. These multifaceted functions underscore HS's importance in maintaining cellular homeostasis and tissue functionality.

2.2. Neurological Implications of HS

In the central nervous system (CNS), HS is indispensable for normal neurological function. It contributes to synaptic plasticity, a process essential for learning and memory, by regulating the availability of growth factors and modulating receptor-ligand interactions at synaptic junctions[13]. HS also participates in axonal guidance during neural development, ensuring precise neuronal connectivity by interacting with guidance molecules such as netrins and semaphorins[14]. Furthermore, HS facilitates neural repair by modulating the activity of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), which are vital for neuronal survival and regeneration[15].

Disruptions in HS synthesis or degradation are implicated in various neurological disorders. In AD, alterations in HS's structure or metabolism can disturb synaptic function, impairing neural communication and exacerbating cognitive decline[4]. These findings highlight HS as a crucial mediator in maintaining CNS health and a potential target for therapeutic interventions.

2.3. Role in Neuroinflammation and Cellular Crosstalk

HS significantly influences immune and inflammatory responses within the CNS. By binding to cytokines, chemokines, and growth factors, HS acts as a reservoir and modulator of inflammatory signaling molecules[3]. It can also function as a co-receptor for toll-like receptors (TLRs) and other immune receptors, fine-tuning the activation of signaling cascades involved in innate immunity[16].

Under pathological conditions such as AD, dysregulated HS metabolism amplifies chronic neuroinflammation. This is particularly evident in its ability to enhance microglial activation, promoting the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)[4]. Moreover, HS-mediated interactions between neurons, glial cells, and the ECM exacerbate cellular crosstalk dysfunction, further contributing to the neurodegenerative process[13]. These insights underscore the dual role of HS in inflammation-both as a regulator under normal conditions and as an amplifier of pathological processes when dysregulated.

Heparan Sulfate in Alzheimer's Pathology: Mechanistic Insights

3.1. Amyloid-beta Dynamics

One of the hallmark features of AD is the accumulation of amyloid-beta (Aβ) plaques in the brain. HS plays a critical role in this process by directly binding Aβ peptides, stabilizing oligomeric forms, and facilitating fibril nucleation and aggregation[11]. This interaction is primarily mediated through the sulfation patterns on HS chains, which determine their binding affinity for Aβ[3]. Interestingly, recent studies suggest that modifying HS sulfation patterns or enzymatically degrading HS chains can disrupt these interactions, thereby inhibiting Aβ aggregation[3]. For instance, heparin analogs and HS mimetics have shown promise in reducing Aβ deposition in experimental models[13]. Such strategies offer a novel therapeutic avenue, focusing on modulating the pathological interactions between HS and Aβ to attenuate plaque formation and its associated neurotoxicity.

3.2. Tau Protein and Microtubule Stability

Another key pathological feature of AD is the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein. HS interacts with tau via heparan sulfate proteoglycans (HSPGs), facilitating its pathological aggregation and propagation across neuronal networks[6]. These interactions also destabilize microtubule structures, disrupting intracellular transport and contributing to neuronal dysfunction[15]. Therapeutic strategies targeting the HS-tau axis include the development of small molecules or antibodies that inhibit HSPG-tau binding, thereby reducing tau seeding and spread[4]. Such interventions hold promise in mitigating tauopathy and its downstream effects on neuronal integrity and function.

3.3. Neuroinflammatory Amplification

Chronic neuroinflammation is a prominent feature of AD, and HS plays a central role in amplifying this process. HS influences microglial activation by modulating receptor–ligand interactions involved in inflammatory signaling[16]. It also regulates the availability of cytokines and chemokines in the ECM, creating a pro–inflammatory milieu that exacerbates neuronal damage[3]. Experimental studies have demonstrated that interventions targeting HS can attenuate neuroinflammatory responses. For example, reducing HS sulfation levels or blocking its interaction with pro–inflammatory mediators has been shown to decrease microglial activation and cytokine release in AD models[13]. These findings highlight the therapeutic potential of HS–targeted approaches in modulating neuroinflammation and providing neuroprotection.

3.4. Vascular Contributions to AD

The integrity of the blood–brain barrier (BBB) is essential for CNS homeostasis, and HS is a key component of the glycocalyx that lines the endothelial cells of the BBB[10]. HS contributes to the structural and functional stability of the BBB by interacting with junctional proteins and regulating vascular permeability[15]. In AD, altered HS expression and structure compromise BBB integrity, allowing neurotoxic substances, such as circulating Aβ and inflammatory mediators, to infiltrate the brain[6]. This exacerbates neuronal injury and inflammation, accelerating disease progression. Therapeutic strategies aimed at restoring HS levels or mimicking its protective functions within the glycocalyx may help reinforce BBB integrity and mitigate AD–related vascular dysfunction[4].

Therapeutic Opportunities for Heparan Sulfate in Modern and Traditional Medicine

4.1. Advances in Modern Therapeutics

4.1.1. HS Mimetics and Enzyme Inhibitors

Recent advancements in synthetic biology have enabled the development of HS mimetics and enzyme inhibitors that selectively target HS–related pathways[11]. These compounds mimic the structural and functional properties of natural HS, allowing them to competitively bind to amyloid–beta (Aβ) and tau proteins, thus disrupting pathological aggregation processes[3]. Additionally, inhibitors of heparanase, the enzyme responsible for HS degradation, have shown promise in stabilizing extracellular matrix integrity and reducing neuroinflammation[13]. Preclinical studies demonstrate that these approaches can mitigate Aβ deposition, tau hyperphosphorylation, and subsequent neuronal damage, offering a novel therapeutic strategy for AD[4,5].

4.1.2. Drug Delivery Innovations

Advances in nanotechnology have revolutionized drug delivery systems, particularly for HS modulators[17]. Nanocarriers such as liposomes, polymeric nanoparticles, and dendrimers have been engineered to encapsulate HS–based therapeutics, providing targeted delivery to specific regions of the brain while minimizing systemic exposure[18]. These systems enhance bioavailability, protect the active compounds from enzymatic degradation, and reduce off–target effects, thereby improving the therapeutic index. For instance, nanoparticles conjugated with HS mimetics have demonstrated efficacy in crossing the blood–brain barrier (BBB), enabling precise modulation of Aβ and tau pathways in AD models[19].

4.1.3. Combination Therapies

Integrating HS–targeted therapies with conventional treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, offers the potential to enhance therapeutic outcomes[20]. This combinatory approach can address multiple facets of AD pathology simultaneously, including synaptic dysfunction, neuroinflammation, and protein aggregation. Furthermore, HS–based therapies could complement emerging modalities like monoclonal antibodies targeting Aβ and tau, potentially reducing the dosage requirements and associated side effects of these treatments[16]. Future clinical trials exploring such synergies are critical for translating these strategies into effective treatments[4].

4.2. Tapping into Korean Medicines

4.2.1. Neuroprotective Herbal Compounds

Korean Medicines (KM) provides a rich repository of herbal remedies with potential neuroprotective properties[21]. Herbs such as Gastrodia elata and Poria cocos have been extensively studied for their anti–inflammatory, antioxidant, and neuroprotective effects [22,23]. These compounds may exert their therapeutic effects by modulating HS–mediated pathways. For example, Gastrodia elata contains active components like gastrodin, which has been shown to attenuate neuroinflammation and oxidative stress[23], while Poria cocos polysaccharides may stabilize HS structures within the extracellular matrix, preserving neural integrity[22].

ISSN 2799-2977, E-ISSN 2799-4066
http://dx.doi.org/10.2305/ackm.2024.6.2.33

4.2.2. Metabolomic Insights

The application of metabolomics to KM offers a cutting-edge approach to uncovering novel compounds that regulate HS biosynthesis and degradation[25]. By analyzing the metabolic profiles of traditional herbs, researchers can identify bioactive molecules that influence HS-related pathways. For instance, advanced metabolomic techniques have revealed specific secondary metabolites in Panax ginseng that interact with glycosaminoglycan metabolism[26]. Such insights not only provide a scientific basis for KM but also facilitate the integration of these compounds into modern therapeutic frameworks[21].

Challenges and Future Directions

5.1. Target Specificity

While HS-based therapies hold immense promise, their broad physiological roles pose a significant challenge[3]. HS interacts with numerous biomolecules across various pathways, making it difficult to selectively target AD-related mechanisms without disrupting essential biological functions[11]. The development of highly specific modulators that can precisely influence Aβ and tau interactions or neuroinflammatory processes is imperative[17]. Advances in structural biology and computational modeling could aid in designing compounds with enhanced specificity[18].

5.2. Integration of TKM with Modern Medicine

Bridging the gap between traditional remedies and contemporary scientific methodologies remains a critical hurdle[21]. Standardizing KM formulations to ensure consistent quality, potency, and safety is essential for clinical application[27]. Additionally, rigorous clinical trials are necessary to validate the efficacy of TKM-derived compounds in AD treatment[28]. Establishing a multidisciplinary research framework that combines KM principles with modern drug discovery techniques could accelerate this integration, paving the way for innovative therapeutic strategies[25].

5.3. Exploring Multi-Targeted Approaches

Given the multifactorial nature of AD, single-target therapies are often insufficient to halt disease progression[4]. Comprehensive strategies that address Aβ aggregation, tau hyperphosphorylation, chronic neuroinflammation, and vascular dysfunction are essential[16]. HS-targeted therapies, due to their involvement in multiple pathological processes, are well-suited for such multi-targeted approaches[29]. Future research should focus on developing combination therapies that synergistically target these pathways, supported by advanced preclinical models and systems biology approaches to predict therapeutic efficacy[30].

Conclusion

Heparan sulfate (HS) occupies a central role in Alzheimer's Disease (AD) pathophysiology, intricately influencing amyloid-beta (Aβ) deposition, tau protein aggregation, and the modulation of neuroinflammatory responses. Its diverse interactions within the extracellular matrix (ECM) and cellular microenvironment underscore its significance as a pivotal mediator in disease progression. Understanding HS's multifaceted roles opens new avenues for therapeutic intervention. Incorporating traditional therapeutic perspectives from KM with cutting-edge HS-based strategies presents an unprecedented opportunity to transform the therapeutic landscape of AD. KM offers a rich repository of neuroprotective herbal remedies and holistic approaches that may synergize with modern scientific innovations to address multiple facets of AD pathology simultaneously.

The potential for collaborative research bridging these disciplines is immense. By integrating KM's centuries-old insights with molecular and biochemical advancements, researchers can develop innovative, multidimensional strategies to combat this multifactorial disorder. This interdisciplinary approach holds promise not only for advancing AD treatment but also for enriching our understanding of the disease's complex mechanisms and expanding the global repertoire of neurodegenerative therapies.

Acknowledgement

This research was supported by "Regional Innovation Strategy (RIS)" through the National Research Foundation of Korea(NRF) funded by the Ministry of Education(MOE)(2023RIS-008)

Conflict of interest

The authors declare no conflict of interest.

References

1. Brookmeyer, R., Abdalla, N., Kawas, C. H., & Corrada, M. M.Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. Alzheimer's & Dementia. 2018;14(2):121-129.
2. Yiannopoulou, K. G., & Papageorgiou, S. G. Current and future treatments for Alzheimer's disease. Therapeutic advances in neurological disorders. 2013; 6(1):19-33.
3. Sarrazin, S., Lamanna, W. C., & Esko, J. D. (2011). Heparan sulfate proteoglycans. Cold Spring Harbor Perspectives in Biology. 2011;3(7): a004952.
4. Reed, M. J., Damodarasamy, M., & Banks, W. A. The extracellular matrix of the blood-brain barrier: structural and functional roles in health, aging, and Alzheimer's disease. Tissue barriers. 2019;7(4): 1651157.
5. Ozsan McMillan, I., Li, J. P., & Wang, L. Heparan sulfate proteoglycan in Alzheimer's disease: aberrant expression and functions in molecular pathways related to amyloid-β metabolism. American journal of physiology. Cell physiology. 2023;324(4) :C893-C909.
6. Iqbal, I., Saqib, F., Mubarak, Z., Latif, M. F., Wahid, M., Nasir, B., Shahzad, H., Sharifi-Rad, J., & Mubarak, M. S. Alzheimer's disease and drug delivery across the blood-brain barrier: approaches and challenges. European journal of medical research, 2024;29(1):313.
7. Alavi Naini, S. M., & Soussi-Yanicostas, N. Heparan Sulfate as a Therapeutic Target in Tauopathies: Insights From Zebrafish. Frontiers in cell and developmental biology.2018;6:163.
8. Yin, H., Liu, R., & Bie, L. (2024). Gastrodin ameliorates neuroinflammation in Alzheimer's disease mice by inhibiting NF-$\varkappa$B signaling activation via PPAR γ stimulation. Aging. 2018;16(10):8657-8666.
9. Pan, X., Chen, K., Han, S., Luo, X., Zhang, D., Zhang, H., Zhang, L., Zhou, X., Li, J., Fang, J., Wang, S., & Ye, X. Total Triterpenes of Wolfiporia cocos (Schwein.) Ryvarden & Gilb Exerts Antidepressant-Like Effects in a Chronic Unpredictable Mild Stress Rat Model and Regulates the Levels of Neurotransmitters, HPA Axis and NLRP3 Pathway. Frontiers in pharmacology. 2022;13:793525.
10. Esko, J. D., & Selleck, S. B.Order out of chaos: assembly of ligand binding sites in heparan sulfate. Annual review of biochemistry. 2002;71: 435-471.
11. Xu, D., & Esko, J. D. Demystifying heparan sulfate-protein interactions. Annual review of biochemistry. 2014;83:129-157.
12. Yayon, A., Klagsbrun, M., Esko, J. D., Leder, P., & Ornitz, D. M. Cell surface, heparin-like molecules are required for binding of basic fibroblast growth factor to its high affinity receptor. Cell. 1991;64(4): 841-848.
13. Fernandez-Vega, I., Lorente-Gea, L., Martin, C., & Quiros, L. M. Heparan sulfate proteoglycans as possible diagnostic molecular tools with therapeutic potential in Alzheimer´s disease. Neural regeneration research. 2021; 16(7):1404-1405.
14. Yamaguchi Y. Heparan sulfate proteoglycans in the nervous system: their diverse roles in neurogenesis, axon guidance, and synaptogenesis. Seminars in cell & developmental biology. 2001;12(2):99-106.
15. Turnbull, J., Powell, A., & Guimond, S. Heparan sulfate: decoding a dynamic multifunctional cell regulator. Trends in cell biology. 2001;11(2): 75-82.
16. Taylor, K. R., & Gallo, R. L. Glycosaminoglycans and their proteoglycans: host-associated molecular patterns for initiation and modulation of inflammation. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2006;20(1):9-22.
17. Fonseca-Santos, B., Gremiao, M. P., & Chorilli, M. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease. International journal of nanomedicine. 2015;10:4981-5003.
18. Hu, H., Huang, Y., Mao, Y., Yu, X., Xu, Y., Liu, J., Zong, C., Boons, G. J., Lin, C., Xia, Y., & Zaia, J. A computational framework for heparan sulfate sequencing using high-resolution tandem mass spectra. Molecular & cellular proteomics : MCP. 2014;13(9): 2490-2502.
19. Prasanna, P., & Upadhyay, A. (2021). Flavonoid-Based Nanomedicines in Alzheimer's Disease Therapeutics: Promises Made, a Long Way To Go. ACS pharmacology & translational science. 2021;4(1): 74-95.
20. Ibrahim, M. M., & Gabr, M. T. (Multitarget therapeutic strategies for Alzheimer's disease. Neural regeneration research. 2019;14(3):437-440.
21. Jeon, S. G., Song, E. J., Lee, D., Park, J., Nam, Y., Kim, J. I., & Moon, M. (2019). Traditional Oriental Medicines and Alzheimer's Disease. Aging and disease. 2019;10(2):307-328.
22. Zhou, X., Zhang, Y., Jiang, Y., Zhou, C., & Ling, Y. Poria cocos polysaccharide attenuates damage of nervus in Alzheimer's disease rat model induced by D-galactose and aluminum trichloride. Neuroreport. 2021;32(8):727-737.
23. Hwang, S. -H., Park, S. -B., Yu, D. -Y., Cho, J. -Y., Lee, W. -W., Park, M. -R., Lee, J. -W., & Jeon,

ISSN 2799-2977, E-ISSN 2799-4066
http://dx.doi.org/10.2305/ackm.2024.6.2.33

Y. -D. Neuroprotective Effect of the Mixture of Gastrodiae elata and Glycyrrhizae uralensis In Vitro. Applied Sciences. 2023;13(1):190.
24. Sharifi-Rad, M., Lankatillake, C., Dias, D. A., Docea, A. O., Mahomoodally, M. F., Lobine, D., Chazot, P. L., Kurt, B., Tumer, T. B., Moreira, A. C., Sharopov, F., Martorell, M., Martins, N., Cho, W. C., Calina, D., & Sharifi-Rad, J. Impact of Natural Compounds on Neurodegenerative Disorders: From Preclinical to Pharmacotherapeutics. Journal of clinical medicine. 2020;9(4):1061.
25. Feng, J., Wang, Y., Xiang, S., Luo, Y., Xu, Y., Wang, Y., Cao, Y., Zhou, M., & Zhao, C. Applying GC-MS based serum metabolomic profiling to characterize two traditional Chinese medicine subtypes of diabetic foot gangrene. Frontiers in molecular biosciences. 2024;11:1384307.
26. Lee, H. J., Jeong, J., Alves, A. C., Han, S. T., In, G., Kim, E. H., Jeong, W. S., & Hong, Y. S.Metabolomic understanding of intrinsic physiology in Panax ginseng during whole growing seasons. Journal of ginseng research. 2019;43(4):654-665.
27. Wang, H., Chen, Y., Wang, L., Liu, Q., Yang, S., & Wang, C. Advancing herbal medicine: enhancing product quality and safety through robust quality control practices. Frontiers in pharmacology. 2023;14:1265178.
28. Pohl, F., & Kong Thoo Lin, P. The Potential Use of Plant Natural Products and Plant Extracts with Antioxidant Properties for the Prevention/Treatment of Neurodegenerative Diseases: In Vitro, In Vivo and Clinical Trials. Molecules. 2018;23(12): 3283
29. Snow, A. D., Cummings, J. A., & Lake, T. The Unifying Hypothesis of Alzheimer's Disease: Heparan Sulfate Proteoglycans/Glycosaminoglycans Are Key as First Hypothesized Over 30 Years Ago. Frontiers in aging neuroscience. 2021;13: 710683.
30. Maramai, S., Benchekroun, M., Gabr, M. T., & Yahiaoui, S. Multitarget Therapeutic Strategies for Alzheimer's Disease: Review on Emerging Target Combinations. BioMed research international. 2020, :5120230.