Review Article

Gastrodia elata Blume (Tianma): Hope for Brain Aging and Dementia

Klaus Heese

Graduate School of Biomedical Science and Engineering, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul 133791, Republic of Korea

Correspondence should be addressed to Klaus Heese; klaus@hanyang.ac.kr

Received 19 August 2020; Revised 26 October 2020; Accepted 3 November 2020; Published 28 December 2020

Copyright © 2020 Klaus Heese. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Since aging-related diseases, including dementia, represent major public health threats to our society, physician-scientists must develop innovative, interdisciplinary strategies to open new avenues for development of alternative therapies. One such novel approach may lie in traditional Chinese medicine (TCM).

Gastrodia elata Blume (G. elata, tianma) is a TCM frequently used for treatment of cerebrocardiovascular diseases (CCVDs). Recent studies of G. elata-based treatment modalities, which have investigated its pharmacologically relevant activity, potential efficacy, and safety, have employed G. elata in well-characterized, aging-related disease models, with a focus on models of aging-related dementia, such as Alzheimer’s disease (AD). Here, I examine results from previous studies of G. elata, as well as related herbal preparations and pure natural products, as prophylaxis and remedies for aging-related CCVDs and dementia. Concluding, data suggest that tianma treatment may be used as a promising complementary therapy for AD.

1. Introduction

Aging-related dementia, which is mediated by damage to brain cells induced by pathways, such as those underlying Alzheimer’s disease (AD), cerebrocardiovascular diseases (CCVDs), and other neurodegenerative diseases (NDs), is causing great inquietude, anxiety, and discomposure in an aging society [1–7]. The World Health Organization (WHO) has recognized the imperative for globally coordinated research to combat dementia [8]. Much hope has been based on use of stem cell-based therapies; however, such approaches still have to overcome major challenges [9].

Thus, with dementia posing a health threat to elderly people, social awareness of healthy lifestyle choices that can prevent aging-related neuroinflammation and cognitive dysfunction has been attracting increasing attention. In particular, a healthy diet, exercise, and caloric restriction have been demonstrated to be preventive against new-onset AD and to effectively ameliorate the symptoms of AD [10, 11]. Familial (early-onset, younger than 65 years) AD is caused by genetic mutations [12–15]. However, the majority of AD cases (~95%) is the sporadic non-inherited form, which is also referred to as late-onset (non-familial, sporadic) AD [14, 16]. Sporadic AD is likely caused by normal aging [16, 17] and its associated consequences, including oxidative stress and disturbance of protein homeostasis [13, 18–20].

Recently, many companies have stopped their AD-related clinical trials and minimized their investments in neurological studies [21]. Therefore, we need new approaches to open doors for alternative therapeutic strategies against aging-related NDs and dementia. In the past few years, alternative medicine has come into focus for the potential to provide new therapeutic measures for dementia [22–25]. Recent comparative proteomics research studies regarding AD-related TCM treatments revealed novel data that suggest potential mechanisms of action of TCM for the prevention of AD pathogenesis involve improving the ubiquitin proteasome system (UPS, including chaperones and cochaperones (notably, heat shock proteins (HSPs) and FK506 binding proteins (FKBPs))) [20, 26]. Particularly, G. elata (tianma) received special attention and will therefore be discussed in more detail as follows [26].
2. *G. Elata* (Tianma) and NDs

*G. elata* (tianma) is a member of the Orchidaceae family and has its origin in East Asia. Its tuber has been used in TCM for centuries [26–30], and extracts of tianma or its active ingredients convey physiological- and health-promoting features, including antitumor, memory improving, and neuroprotective activities [30–33]. Particularly, this TCM has been widely used in Asia to treat dizziness, paralysis, epilepsy [34], and hypertension [35]. Tianma has also been used in this region to overcome cognitive deficits and prevent NDs [30, 36–41], including AD [42–46], vascular dementia (VD) [33, 41], and Parkinson’s disease (PD) [47, 48], with gastrodin and 4-hydroxybenzyl alcohol among the primary active components [48–53].

3. Tianma Mobilizes the Cerebrocardiovascular System

It is common knowledge that heart health contributed to brain health. Connections between AD, VD, diabetes mellitus (type 2, T2DM), and CCVDs have been proposed based on the strong associations between cardiovascular risk factors and AD and VD, suggesting that these diseases share common characteristics [54–57]. The risk of developing aging-related AD, VD, and CCVDs appears to
be increased with a wide range of conditions and lifestyle factors, including global failure of cellular energy metabolism, hypertension, dyslipidemia, hypercholesterolemia, lower physical activity, and poor diet [22, 56, 58–66].

3.1. Tianma Enhances Acetylcholine- (ACh-) Induced Vaso-relaxation, A Measure of the Contractile Force and Elasticity of Aortic Vessels: Vasodilatory Proteomic Profile Changes in Aortic Tissue. Blood vessel tonicity is regulated by vascular smooth muscle cells which modulate contraction and relaxation. Functional aortic tissue proteomic data have demonstrated that long-term treatment with small doses of tianma regulated blood vessel tonicity by mediating the expression of contractile proteins (e.g., actin alpha 2 (ACTA2)) and structural proteins (e.g., desmin (DES), microtubule-associated protein 4 (MAP4), PDZ, and LIM domain 1 (PDLIM1) and vinculin (VCL)), extracellular matrix proteins (ECM, e.g., elastin (ELN), fibulin 5 (FBLN5), and proline- and arginine-rich end leucine-rich repeat protein (PRELP)), and thrombotic proteins (e.g., annexin A2 (ANXA2)), thereby enhancing thoracic aortic contractile force and improving blood vessel elasticity (Figure 1) [67]. Moreover, elevated ANXA2 and reduced level of fatty acid binding protein 4 (FABP4) may prevent atherosclerosis and cardiovascular diseases [68, 69].

By inductive reasoning, tianma could likely prevent many CCVDs, such as headache, hypertension,
atherosclerosis, and stroke, by facilitating vasodilatory effects that strengthen the arterial structure. Therefore, identification of all the bioactive ingredients in tianma could help facilitate its application as an efficient therapeutic herbal medicine for treatment of CCVDs by elucidating the mechanisms by which it ameliorates these abnormal cardiovascular responses [33, 41, 54, 67, 70, 71].

4. Tianma Improves Cognitive Function during Aging-Related Dementia

Accumulating evidence indicates that tianma sharpens several cognitive functions, including memory and learning activities [30, 32, 40, 43, 49]. Moreover, neuroprotective and neuro-regenerative qualities have been attributed to tianma, particularly during aging and aging-related NDs, such as AD, PD, and VD [26, 30, 36, 38–44, 47, 72]. Specifically, pharmacologically relevant studies have demonstrated at the cellular and molecular levels that tianma could prevent AD by modulating proteolytic processing of amyloid beta precursor protein (APP), driving the nonamyloidogenic pathway (Figure 2) [41–44, 46].

5. Discussion

5.1. Aging and Dementia: Abnormal Protein Structures. In AD, accumulation of Aβ and hyperphosphorylated MAPT protein act as seeds for prion-like transmission of misfolded proteins to adjacent neurons, where misfolded MAPT further aggregates into neurofibrillary tangles (NFTs) [73–75]. The FKBP5s act as a cochaperone in AD brains trying to prevent MAPT degradation by binding to MAPT and increasing its stability via interaction with the peptidylprolyl isomerase (PPIase) domain [76, 77]. However, downregulation of important E3-ligases (tripartite motif containing 32/37 (TRIM32/37)) and chaperone proteins, such as HSPs (e.g., HSP90), might impair hyperphosphorylated MAPT clearance [20, 37]. HSP90 and STUB1 (STIP1 (stress-induced phosphoprotein1) homology and U-box containing protein 1, also known as carboxyl terminus of heat shock cognate 70-(HSC70-) interacting protein (CHIP)), target hyperphosphorylated MAPT for proteasomal degradation. Hyperphosphorylated MAPT loses its physiological function for axonal transport, aggregates into NFTs, and causes neuron death. In addition, the impaired UPS (consisting of the 26S proteasome, ubiquitin ligases, and ubiquitin hydrolases) and compromised function of HSPs and FKBP5s together impair the protein degradation pathway and promote pathophysiological conditions [20, 26, 37].

5.2. Interference Prevents Protein Misfolding during Aging and in NDs. The proposed pathomechanism underlying AD involves Aβ plaque formation, NFTs, and deregulation of chaperone proteins. Consequently, in AD brains, an impaired UPS system is thought to account for Aβ aggregation and hyperphosphorylated MAPT-mediated NFT formation, which is potentially furthered by an irregular APP intracellular domain (AICD) signaling pathway [20]. The various protein groups modulated by tianma treatment affect the UPS system, and active tianma ingredients also target molecular chaperones and cochaperones, such as HSPs and FKBP5, and modulate the actions of protein phosphate PP2A. Together, these data open new avenues for future investigations into the prophylactic effects of tianma for aging-related dementia and NDs (Figure 2(d)) [20, 26].

6. Conclusion

The human brain, with its high-level cognitive functions, requires a large degree of flexibility and adaptability for appropriate learning and memory and is very vulnerable to cerebrovascular injuries, such as ischemia or stroke, which can cause NDs and dementia. Tianma has been shown in human clinical studies to be effective against VD [40], and various pre-clinical studies have demonstrated at the molecular and cellular levels its potential as an efficacious anti-aging elixir.

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| Aβ           | Amyloid beta peptide |
| ACh          | Acetylcholine |
| ACTA2        | Actin alpha 2 |
| AD           | Alzheimer’s disease |
| AICD         | APP intracellular domain |
| ANXA2        | Annexin A2 |
| APP          | Amyloid beta precursor protein |
| BACE1        | Beta-secretase 1 |
| CCVD         | Cerebrocardiovascular disease |
| DES          | Desmin |
| DM           | Diabetes mellitus |
| ELISA        | Enzyme-linked immunosorbent assay |
| ELN          | Elastin |
| EOAD         | Early-onset AD |
| FABP4        | Fatty acid binding protein 4 |
| FBLN5        | Fibulin 5 |
| FKBP         | FK506 binding protein |
| G. elata     | Gastrodia elata Blume |
| HSP90        | Heat shock cognate 70 |
| LOAD         | Late-onset (nonfamilial, sporadic) AD |
| MAP4         | Microtubule-associated protein 4 |
| MAPT         | Microtubule-associated protein tau |
| ND           | Neurodegenerative disease |
| NFT          | Neurofibrillary tangles |
| PD           | Parkinson’s disease |
| PDLIM1       | PDZ and LIM domain 1 |
| PDZ          | Postsynaptic density protein (PSD95) |
| Dlg1         | Drosophila disc large tumor suppressor |
| zo-1         | zonula occludens-1 protein |
| LIM          | Lin11, Isl-1, Mec-3 |
| PE           | Phenylephrine |
| PPIase       | Peptidylprolyl isomerase |
| PRELP        | }
Proline- and arginine-rich end leucine-rich repeat protein
STIP1: Stress-induced phosphoprotein 1
STUB1: STIP1 homology and U-box containing protein 1
TCM: Traditional Chinese medicine
TRIM: Tripartite motif containing
UPS: Ubiquitin proteasome system
VCL: Vinculin
VD: Vascular dementia
WHO: World Health Organization.

Conflicts of Interest
The author declares no conflicts of interest.

Acknowledgments
This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), which was funded by the Ministry of Education (2019R1F1A1056445).

References
[1] K. Nagata, T. Yamazaki, D. Takano et al., “Cerebral circulation in aging,” Ageing Research Reviews, vol. 30, pp. 49–60, 2016.
[2] L. Pini, M. Pievani, M. Bocchetta et al., “Brain atrophy in alzheimer’s disease and aging,” Ageing Research Reviews, vol. 30, pp. 25–48, 2016.
[3] S. Tarantini, C. H. T. Tran, G. R. Gordon, Z. Ungvari, and A. Csiszar, “Impaired neurovascular coupling in aging and alzheimer’s disease: contribution of astrocyte dysfunction and endothelial impairment to cognitive decline,” Experimental Gerontology, vol. 94, pp. 52–58, 2017.
[4] M. Vijayan, S. Kumar, J. S. Bhatti, and P. H. Reddy, “Molecular links and biomarkers of stroke, vascular dementia, and alzheimer’s disease,” Progress in Molecular Biology and Translational Science, vol. 146, pp. 95–126, 2017.
[5] T. Wyss-Coray, “Ageing, neurodegeneration and brain rejuvenation,” Nature, vol. 539, no. 7628, pp. 180–186, 2016.
[6] T. Yang, Y. Sun, Z. Lu, R. K. Leak, and F. Zhang, “The impact of cerebrovascular aging on vascular cognitive impairment and dementia,” Ageing Research Reviews, vol. 34, pp. 15–29, 2017.
[7] J. P. da Costa, R. Vitorino, G. M. Silva, C. Vogel, A. C. Duarte, and T. Rocha-Santos, “A synopsis on aging-theories, mechanisms and future prospects,” Ageing Research Reviews, vol. 29, pp. 90–112, 2016.
[8] H. Shah, E. Albanese, C. Duggan et al., “Research priorities to reduce the global burden of dementia by 2025,” The Lancet Neurology, vol. 15, no. 12, pp. 1285–1294, 2016.
[9] S. Pramanik, Y. A. Sulistio, and K. Heese, “Neurotrophin signaling and stem cells implications for neurodegenerative diseases and stem cell therapy,” Molecular Neurobiology, vol. 54, no. 9, pp. 7401–7459, 2017.
[10] A. M. McGrattan, B. McGuinness, M. C. McKinley et al., “Diet and inflammation in cognitive ageing and alzheimer’s disease,” Current Nutrition Reports, vol. 8, no. 2, pp. 53–65, 2019.
[11] G. K. Bhatti, A. P. Reddy, P. H. Reddy, and J. S. Bhatti, “Lifestyle modifications and nutritional interventions in aging-associated cognitive decline and alzheimer’s disease,” Frontiers in Aging Neuroscience, vol. 11, p. 369, 2019.
[12] D. J. Selkoe, “Alzheimer’s disease: genes, proteins, and therapy,” Physiological Reviews, vol. 81, no. 2, pp. 741–766, 2001.
[13] K. Heese and H. Akatsu, “Alzheimers disease-an interactive perspective,” Current Alzheimer Research, vol. 3, no. 2, pp. 109–121, 2006.
[14] R. E. Tanzi and L. Bertram, “New frontiers in alzheimer’s disease genetics,” Neuron, vol. 32, no. 2, pp. 181–184, 2001.
[15] L. M. Bekris, C.-E. Yu, T. D. Bird, and D. W. Tsuang, “Review article: genetics of alzheimer disease,” Journal of Geriatric Psychiatry and Neurology, vol. 23, no. 4, pp. 213–227, 2010.
[16] C. Reitz and R. Mayeux, “Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers,” Biochemical Pharmacology, vol. 88, no. 4, pp. 640–651, 2014.
[17] J. Lindsay, D. Laurin, R. Verreault et al., “Risk factors for alzheimer’s disease: a prospective analysis from the Canadian study of health and aging,” American Journal of Epidemiology, vol. 156, no. 5, pp. 445–453, 2002.
[18] Y. Ibara, M. Morishima-Kawashima, and R. Nixon, “The ubiquitin-proteasome system and the autophagic-lysosomal system in alzheimer disease,” Cold Spring Harbor Perspectives in Medicine, vol. 2, no. 8, p. a006361, 2012.
[19] B. R. Troen, “The biology of aging,” Mount Sinai Journal of Medicine, vol. 70, no. 1, pp. 3–22, 2003.
[20] Y. A. Sulistio and K. Heese, “The ubiquitin-proteasome system and molecular chaperone deregulation in alzheimer’s disease,” Molecular Neurobiology, vol. 53, no. 2, pp. 905–931, 2016.
[21] C. Rowland, The Washington Post, Vol. Business, 209, https://www.washingtonpost.com/business/economy/alzheimers-research-is-getting-a-reboot-at-small-companies-focused-on-the-immune-system/2019/07/03/974d8854-91e9-11e9-b58a-a6a9afa0e3e_story.html.
[22] E. Flanagan, D. Lamport, L. Brennan et al., “Nutrition and the ageing brain: moving towards clinical applications,” Ageing Research Reviews, vol. 62, Article ID 101079, 2020.
[23] Q. Yan, W. Wang, J. Weng et al., “Dissolving microneedles for transdermal delivery of huperzine A for the treatment of alzheimer’s disease,” Drug Delivery, vol. 27, no. 1, pp. 1147–1155, 2020.
[24] A. Balan, M. A. Moga, L. Dima, S. Toma, A. Elena Necula, and C. V. Anastasiu, “Royal jelly-A traditional and natural remedy for postmenopausal symptoms and aging-related pathologies,” Molecules, vol. 25, no. 14, p. 3291, 2020.
[25] X. Deng, S. Zhao, X. Liu et al., “Polygala tenuifolia: a source for anti-alzheimer’s disease drugs,” Pharmaceutical Biology, vol. 58, no. 1, pp. 410–416, 2020.
[26] Y. A. Sulistio and K. Heese, “Proteomics in traditional Chinese medicine with an emphasis on alzheimer’s disease,” Evidence-Based Complementary and Alternative Medicine, vol. 2015, Article ID 393510, 2015.
[27] H.-D. Zhan, H.-Y. Zhou, Y.-P. Sui et al., “The rhizome of gastrodia elata blume-an ethnopharmacological review,” Journal of Ethnopharmacology, vol. 189, pp. 361–385, 2016.
[28] G. K. Bhatti, “Lifestyle and nutritional interventions in gastrodin,” Frontiers in Pharmacology, vol. 9, p. 24, 2018.

[29] L. Shizhen, Bencao Gangmu: Compendium of Materia Medica, Foreign Language Press, Beijing, China, 2006.
[30] Y. Liu, J. Gao, M. Peng et al., “A review on central nervous system effects of gastrodin,” Frontiers in Pharmacology, vol. 9, p. 24, 2018.
Evidence-Based Complementary and Alternative Medicine

[31] J. C. Heo, S. U. Woo, M. Son et al., “Anti-tumor activity of gastrodia elata blume is closely associated with a GTP-Ras-dependent pathway,” Oncology Reports, vol. 18, no. 4, pp. 849–853, 2007.

[32] Y.-M. Park, B.-G. Lee, S.-H. Park et al., “Prolonged oral administration of gastrodia elatextract improves spatial learning and memory of scopolamine-treated rats,” Laboratory Animal Research, vol. 31, no. 2, pp. 69–77, 2015.

[33] J. W. Xian, A. Y. Choi, C. B. Lau, W. N. Leung, C. F. Ng, and C. W. Chan, “Gastrodia and Uncaria (tianma gouteng) water extract exerts antioxidative and antiapoptotic effects against cerebral ischemia in vitro and in vivo,” Chinese Medicine, vol. 11, p. 27, 2016.

[34] L. M. Ojemann, W. L. Nelson, D. S. Shin, A. O. Rowe, and R. A. Buchanan, “Tian ma, an ancient Chinese herb, offers new options for the treatment of epilepsy and other conditions,” Epilepsy & Behavior, vol. 8, no. 2, pp. 376–383, 2006.

[35] X. Xiong, X. Yang, Y. Liu, Y. Zhang, F. Wang, and J. Wang, “Chinese herbal formulas for treating hypertension in traditional Chinese medicine: perspective of modern science,” Hypertension Research, vol. 36, no. 7, pp. 570–579, 2013.

[36] U. Kumari and K. Heese, “Cardiovascular dementia—a different perspective,” Current Neuropharmacology, vol. 14, no. 1, pp. 287–294, 2017.

[37] R. Ha, D. U. Lee, J. T. Lee et al., “4-Hydroxybenzaldehyde from Gastrodia elata B1. is active in the antioxidation and GABAergic neuromodulation of the rat brain,” Journal of Ethnopharmacology, vol. 73, no. 1-2, pp. 329–333, 2000.

[38] E. Picano, R. M. Bruno, G. F. Ferrari, and U. Bonuccelli, “Cognitive impairment and cardiovascular disease: so near, so far,” International Journal of Cardiology, vol. 175, no. 1, pp. 21–29, 2014.

[39] R. Shi, C. B. Zheng, H. Wang et al., “Gastrodin alleviates vascular dementia in a 2-VO-vascular dementia rat model by altering amyloid and tau levels,” Pharmacology, vol. 105, no. 7-8, pp. 386–396, 2020.

[40] M. Li, Y. Du, L. Wang et al., “Efficient discovery of quality control markers for gastrodia elata tuber by fingerprint-ef ficacy relationship modelling,” Phytochemical Analysis, vol. 28, no. 4, pp. 351–359, 2017.

[41] J. H. Ha, D. U. Lee, J. T. Lee et al., “4-Hydroxybenzaldehyde from Gastrodia elata B1. is active in the antioxidation and GABAergic neuromodulation of the rat brain,” Journal of Ethnopharmacology, vol. 73, no. 1-2, pp. 329–333, 2000.

[42] E. Picano, R. M. Bruno, G. F. Ferrari, and U. Bonuccelli, “Cognitive impairment and cardiovascular disease: so near, so far,” International Journal of Cardiology, vol. 175, no. 1, pp. 21–29, 2014.

[43] A. M. Hooghiemstra, A. S. Bertens, A. E. Leeuwis et al., “The missing link in the pathophysiology of vascular cognitive impairment: design of the heart-brain study,” Cerebrovascular Diseases Extra, vol. 7, no. 3, pp. 140–152, 2017.

[44] U. Kumari and K. Heese, “Cardiovascular dementia—a different perspective,” The Open Biochemistry Journal, vol. 4, pp. 29–52, 2010.

[45] R. A. L. De Sousa, A. R. Harmer, D. A. Freitas, V. A. Mendonça, A. C. R. Lacerda, and H. R. Leite, “An update on potential links between type 2 diabetes mellitus and Alzheimer’s disease,” Current Neuropharmacology, 2020, https://www.eurekaselect.com/184274/article.

[46] A. Datta, J. E. Park, X. Li et al., “Phenotyping of anin vitro model of ischemic penumbra by iTRAQ-based shotgun quantitative proteomics,” Journal of Proteome Research, vol. 9, no. 1, pp. 472–484, 2010.

[47] A. Datta, Q. Jingru, T. H. Khor, M. T. Teo, K. Heese, and S. K. Sze, “Quantitative neuroproteomics of an in vivo model of Alzheimer’s disease,” Neural Regeneration Research, vol. 8, no. 12, pp. 1061–1070, 2013.
model of focal cerebral ischemia/reperfusion injury reveals a temporal regulation of novel pathophysiological molecular markers," *Journal of Proteome Research*, vol. 10, no. 11, pp. 5199–5213, 2011.

[61] A. Datta, H. Akatsu, K. Heese, and S. K. Sze, "Quantitative clinical proteomic study of autopsied human infarcted brain specimens to elucidate the deregulated pathways in ischemic stroke pathology," *Journal of Proteomics*, vol. 91, pp. 556–568, 2013.

[62] A. Ahmad, V. Patel, J. Xiao, and M. M. Khan, "The role of neurovascular system in neurodegenerative diseases," *Molecular Neurobiology*, vol. 57, no. 11, pp. 4373–4393, 2020.

[63] Z. Bartochowski, J. Conway, Y. Wallach, B. Chakkamparambil, S. Alakkassery, and G. T. Grossberg, "Dietary interventions to prevent or delay alzheimer’s disease: what the evidence shows," *Current Nutrition Reports*, vol. 9, no. 3, pp. 210–225, 2020.

[64] A. C. van den Brink, E. M. Brouwer-Brolsma, A. A. M. Berendsen, and O. van de Rest, "The mediterranean, dietary approaches to stop hypertension (DASH), and mediterranean-DASH intervention for neurodegenerative delay (MIND) diets are associated with less cognitive decline and a lower risk of alzheimer’s disease-a review," *Advances in Nutrition*, vol. 10, no. 6, pp. 1040–1065, 2019.

[65] F. Pistollato, R. C. Iglesias, R. Ruiz et al., "Nutritional patterns associated with the maintenance of neurocognitive functions and the risk of dementia and Alzheimer’s disease: a focus on human studies," *Pharmacological Research*, vol. 131, pp. 32–43, 2018.

[66] V. Solfrizzi, C. Custodero, M. Lozupone et al., "Relationships of dietary patterns, foods, and micro- and macronutrients with alzheimer’s disease and late-life cognitive disorders: a systematic review," *Journal of Alzheimer’s Disease*, vol. 59, no. 3, pp. 815–849, 2017.

[67] L. Feng, A. Manavalan, M. Mishra, S. K. Sze, J.-M. Hu, and K. Heese, "Tianma modulates blood vessel tonicity," *The Open Biochemistry Journal*, vol. 6, pp. 56–65, 2012.

[68] E. C. Flood and K. A. Hajjar, "The annexin A2 system and vascular homeostasis," *Vascular Pharmacology*, vol. 54, no. 3-6, pp. 59–67, 2011.

[69] M. Furuhashi and G. S. Hotamisligil, "Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets," *Nature Reviews Drug Discovery*, vol. 7, no. 6, pp. 489–503, 2008.

[70] I. Ferrer, "Cognitive impairment of vascular origin: neuropathology of cognitive impairment of vascular origin," *Journal of the Neurological Sciences*, vol. 299, no. 1-2, pp. 139–149, 2010.

[71] T. Tarumi and R. Zhang, "Cerebral blood flow in normal aging adults: cardiovascular determinants, clinical implications, and aerobic fitness," *Journal of Neurochemistry*, vol. 144, no. 5, pp. 595–608, 2018.

[72] A. Manavalan, L. Feng, S. K. Sze, J.-M. Hu, and K. Heese, "New insights into the brain protein metabolism of gastrodia elata-treated rats by quantitative proteomics," *Journal of Proteomics*, vol. 75, no. 8, pp. 2468–2479, 2012.

[73] D. M. Walsh and D. J. Selkoe, "Amyloid β-protein and beyond: the path forward in alzheimer’s disease," *Current Opinion in Neurobiology*, vol. 61, pp. 116–124, 2020.

[74] A. A. Mamun, M. S. Uddin, B. Mathew, and G. M. Ashraf, "Toxic tau: structural origins of tau aggregation in alzheimer’s disease," *Neural Regeneration Research*, vol. 15, no. 8, pp. 1417–1420, 2020.