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Mini review

Some characteristics and functional properties of Chunma *(Gastrodia elata)* as a food supplement: a short review

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Abstract

Gastrodin elata blume (Tianma in Chinese, Chunma in Korean) is a perennial parasitic herbaceous plant native to Korea, Japan and China (Chae *et al.*, 2008). The plant has recently received very good attention, especially in Korea, due to its excellent health-promoting properties. This plant is reported to have excellent antioxidant, anticancer and anti-inflammatory properties. This paper briefly reviews some characteristics and functional properties of Chunma.

Introduction

Gastrodin elata blume (Tianma in Chinese, Chunma in Korean) is a perennial parasitic herbaceous plant native to Korea, Japan and China (Chae *et al.*, 2008). It belongs to the family Orchidaceae and grows symbiotically with *Armillaria mella* (Kim *et al.*, 2005). The dry tuber has been traditionally described in the treatment of headache, migraine, dizziness, epilepsy, rheumatism, neuralgia, paralysis and other neuralgic and nervous disorders in eastern Asian medicine for more than 2000 years (Tang and Eisenbrand, 1992; Hsieh *et al*., 2001; Bensky *et al*., 2004; Chae *et al*., 2008; Xue *et al*., 2013). Sedation, anti- convulsion and anti- epilepsy activities have been associated with the herb (Lin *et al.*, 2008).

Analysis of *G. elata* has identified several constituents present in the plant (Kim *et al.*, 2005). Most of the constituents are phenolic compounds such as phenolic glycosides, sulfurous phenolic compounds and organic acids, sugars, B- sitosterol, sterols, cholesterol, p- hydroxyl benzyl alcohol, p- hydroxybenzaldehyde and vanillin (Zhou *et al.*, 1979; Taguchi *et al*., 1981; Noda *et al*., 1995; Wu *et al*., 1996; Hsieh *et al.*, 1997; Hayashi *et al.*, 2002; Liu *et al*., 2002). Among the compounds, three phenolic glycosides were identified from *G. elata*: gastrodin, parishin and parishin B (Chae *et al.*, 2008).

In an attempt to validate its long pharmaceutical use in traditional Chinese medicine, several reports study the activity of *G. elata* extracts, decoctions and isolated compounds. The biological activities of *G. elata* extracts using different solvents are well documented. The aqueous extract of *G. elata* improved memory loss in mice and cured vasoneural headache (Hsieh *et al*., 1997), improved performance deficit in senescent mice (Hsieh *et al*., 1997) and has been reported to have scavenging activities (Liu and Mori, 1993; Hsieh *et al*., 1997). Decreased dopamine was observed in rat brains administered with *G. elata* (Hsieh *et al.*, 1997). Meanwhile, the methanol extract of *G. elata* improved scopolamine – induced deficit in rats (Wu *et al.*, 1996), and prevented PC 12 cell apoptosis (Huang *et al*., 2004). The ethanolic extract

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of *G. elata* fermented with *Lactobacillus brevis* increased sleep when administered in mice (Lee *et al.,* 2013). The mixture works by inhibiting the receptor antagonist to the benzodiazepine receptor of the mice orifice (Lee *et al*., 2013). The ethyl ether fraction reduced neuronal death in neuroblastoma cells (Kim *et al*., 2003), while the ether fraction attenuates decrease in GABA and glutamate content (Ha *et al*., 2000) and exhibits anti- convulsant effects (Huh *et al*., 1995). *G. elata* also reportedly inhibited glutamate-induced apoptosis in neuron cells (Lee *et al*., 1999), reduces lipid peroxide levels (Liu and Mori, 1993) and protects against brain injury induced by transient ischemia (Yu *et al*., 2005). A decoction of *G. elata* and uncaria exerts interesting pharmacological activity on neurodegenerative diseases (Chik *et al.*, 2013). This paper briefly reviews some characteristics and functional properties of Chunma.

Gastrodin

Gastrodi (p-hydroxymethylphenyl-b-D-glucopyranoside) is the major active compound found in *G. elata,* constituting almost 0.3%- 1.97% of *G. elata* (Li *et al*., 2001; Chae *et al*., 2008). The molecular formula of gastrodin is $C_{13}H_{18}O_7$ with a molecular weight of 286.28 (Lin *et al*., 2008). It was first described by Baek *et al*. (1999) as the compound responsible for anticonvulsive effect in *G. elata* and has since been reported as the most active constituent in *g. elata* (Zhao *et al*., 1999). Gastrodin is listed as an index component in Chinese Pharmacopoeia (Yang *et al*., 2001; Ong *et al*., 2007; Chae *et al.*, 2008) and was approved for safe use by the Korean Food and Drug Administration in 2000.

Neuroprotective

Anti- inflammatory and anti-oxidant

The molecular structure of gastrodin and HBA containing at least one aromatic ring with one or more hydroxyl groups attached reflect their capability to interact with radicals to eliminate them (Chik *et al.*, 2013). Several studies report the strong antioxidant activity of gastrodin. Evidence shows that neurodegenerative diseases such as Parkinson's disease, stroke, brain trauma etc. are facilitated by oxidative stress, inflammation and apoptosis of neuron cells. Oxidative stress is the result of the inability of cells to effectively eliminate ROS generated in the cells, which promote membrane lipid peroxidation and DNA fragmentation, resulting in cell death (Beckman and Crowe, 1993; Simonian and Coyle, 1996; Choi *et al*., 1998; Zhang *et al*., 2002). Gastrodin effectively acts on these mechanisms through its anti-oxidant and anti- inflammatory properties.

Gastrodin has been reported to increase the expression of antioxidant proteins, attenuate inflammatory response and decrease lipid peroxidation in the brain (Yong *et al.*, 2009; Kumar *et al*., 2013; Peng *et al*., 2015; Li and Zhang, 2015). Furthermore, gastrodin's antioxidant activity decreases the expression level of neurotoxic proinflammatory mediators in microglial cells which are responsible for general neuronal injury, or more chronic neurodegenerative brain disorders such as Parkinson's disease and Alzheimer's disease (Dai *et al*., 2011; Zong *et al*., 2011; Zhao *et al*., 2012; Li *et al.*, 2012; Yang *et al*., 2013; Kumar *et al*., 2013; Wang *et al.*, 2014; Jiang *et al*., 2014). Gastrodin has been described as a well- known natural calcium channel blocker (Li and Ma, 2014); high calcium influx through calcium channels is a trigger leading to cell death (Zeng *et al.*, 2006; Liu *et al*., 2009).

Analgesic

Gastrodin has been reported as an effective analgesic, relieving trigeminal neuralgia, migraine and vascular headache (Zhu *et al*., 2006). It inhibits the acid- sensing ion channels which are responsible for mediating pain (Qiu *et al.*, 2014). Additionally, gastrodin attenuates mechanical allodynia and thermal hyperalgesia mediated by reversing the potassium currents, regulating neuron hyper excitability responsible for painful diabetic neuropathy (Sun *et al.*, 2012).

Cardioprotective

Traditional uses of *G. elata* indicate its usefulness in treating cardiovascular conditions such as hypertension (Wang *et al*., 2007; Zhang *et al.*, 2008). Scientific reports of the cardiovascular- protective effects of gastrodin have been reported. Shu *et al.* (2011) describe the mechanism of cardiovascular protection of gastrodin. Gastrodin prevented cardiac hypertrophy mediated by ERK ½ signalling and GATA-4 activation (Shu *et al*., 2011). They further report that gastrodin protects against fibrosis (Sun *et al.*, 2011).

Anticancer immunomodulatory

Gastrodin upregulates the anti- cancer immune response and represses tumor growth in a study by Shu *et al.* (2012). In this study comparing the anti-hepatocellular carcinoma activity of gastrodin, vanillin and parishin *in vivo*, only gastrodin showed significant anticancer activity (Shu *et al*., 2012). The results of this study suggest that gastrodin was more effective and less toxic compared to standard

treatment using cisplatin in the repression of hepatic ascetic tumor cell growth in mice (Shu *et al.*, 2012).

Extraction of gastrodin

Traditionally, gastrodin was obtained via extraction of *G. elata* rhizomes and flowers. Soxhlet extraction methods using methanol and pressurized liquid extraction have been reported with good extraction efficiencies (Ong *et al*., 2007). Besides classic solvent methods, greener and safer methods have been described. Kim *et al.* (2005) describe an extraction method using enzymes to facilitate high yield of extraction while minimizing solvent use. However, traditional extraction from *G. elata* is becoming less attractive because not only is it time-consuming, but also costly, with low yields (0.1%). Moreover, wild *G. elata* is fast depleting due to the excessive collection (Bai *et al*., 2016). Therefore, synthesis of gastrodin has been explored by researchers and industries.

Chemical synthesis of gastrodin

Zhou *et al.* (1980) reported the first successful chemical synthesis of gastrodin (Zhou *et al.*, 1980) followed by Jie and Guo in 1984. However, these methods depended on the heavy use of toxic materials and had low yields. Li and Ma (2014) describe an improved chemical synthesis of gastrodin using a simple, high yield, cost- effective and less toxic process. Analogues of gastrodin in the form of aryl glycosides have also been synthesized (Xue *et al.*, 2013). Several patents describing the chemical synthesis of gastrodin have been filed (CN 104744529, BCN 103275146 A, CN 102516329 B, CN 102977161 A).

Despite the availability of methods describing the chemical synthesis of gastrodin, these procedures are unattractive for several reasons. Most chemical procedures are highly complex (Ducros *et al*., 2003; Peng *et al*., 2007), utilize high amounts of toxic and expensive solvent, and do not go past laboratory scale (Li and Ma, 2014). There is also the risk of trace reagents being present in the final product, making it unsuitable for human consumption (Ducros *et al.*, 2003). Gastrodin is a phenolic glycoside, which is part of the glycoconjugate family, which represents one of the most difficult compounds in nature to synthesize chemically (Ducros *et al.*, 2003). Glycosyltransferases are part of a large family of enzymes that are responsible for the synthesis of glycoconjugates in nature (Breton *et al.*, 2005). Natural and recombinant glycosyltransferases are continuously being studied as a route for successful biosynthesis of glycoconjugates for use in drug therapies.

Enzymatic/ microbial synthesis

Whole- based systems using fungi and bacteria for producing natural glycosyltransferases have been reported. Hai- Feng *et al*. (2008) and Zhang *et al*. (2008) describe the biotransformation of HBA into gastrodin using *A. luteo-virens* Sacc U; a selective and highly reactive method for a similar biotransformation process was described using *Rhizopus chinensis* SAITO AS3.1165 by Zhu *et al*. (2010). The use of fungi *Aspergillus foetidus* ZU-G1 and *Penicillium cyclopium* AS 3.4513 have also been reported (Fan *et al*., 2013). In their work, Zhu *et al.* (2010) identify the enzyme responsible for this biotransformation as gastrodin biosynthesis enzyme (GBE), a glycosyltransferase. Niu *et al.* (2016) described an improved gastrodin production based on the work by Zhang *et al*. (2008) using cell culture *Armillari luteo- virens* Sacc.. Most recently, a method for *de novo* biosynthesis of gastrodin in *E. coli* was described by Bai *et al*. (2016). The method uses glucose as the substrate and suridine sugar glycosyltransferase (UGT) to catalyse the process. The work is described to be more environmentally friendly and is easily scaled up. For the synthesis of HBA, biotransformation of gastrodin using the fungus Mucor spinosus strain 3.3450 has been reported (Jixun *et al.*, 2001).

Pharmacokinetics

Methods for the detection and analysis of gastrodin content are essential in order to understand the pharmacokinetics of gastrodin in the body. Li *et al.* (2006) first described a LC-UV method for detecting gastrodin in dog plasma. This was followed by the study of Zhang *et al.* (2008) reporting LC-MS for the analysis of gastrodin and HBA from oral administration of *g. elata*. Due to their activity on the CNS, there is interest in analysing the presence of gastrodin and HBA in the brain and thereafter its excretion in the bile and urine. Lin *et al*. (2008) analysed gastrodin and HBA in blood, bile and brain using a microdialysis and LC-MS/MS method. Wang *et al.* (2008) then examined the distribution of gastrodin in rat brain using an improved HPLC-UV method. Most recently, Jiang *et al.* (2013) developed a method for simultaneous detection of gastrodin and puerarin in rat plasma via HPLC.

When administered in rats, gastrodin is rapidly taken up in the central nervous system (Wang *et al*., 2007). It then rapidly enters the blood- brain barrier (BBB) and is decomposed into HBA in the liver, blood and brain (Lu *et al.*, 1985; You *et al.*, 1994; Hsieh *et*

al., 1997). HBA has similar pharmacological effects to gastrodin (Wu *et al*., 1996). Peak concentration in the brain and bile was reached 10-20 minutes after administration of gastrodin in rats (Lin *et al*., 2007). Both gastrodin and HBA are able to pass through the blood- brain barrier, especially accumulating in the cerebellum the highest, where it exerts neurological effects (Lu *et al*., 1985, You *et al.*, 1994, Wang *et al*., 2007). However, this penetration through the blood-brain barrier is poor due to the hydrophilic activity of gastrodin. This suggests that a small amount of gastrodin delivered through the BBB has significant impact on the CNS (An *et al*., 2003; Lin *et al*., 2007). Gastrodin immediately undergoes biliary excretion after 15 min, but is also excreted unchanged in the urine (Lu *et al*., 1985; Meljer *et al*., 1990; Lin *et al*., 2007). Jiang *et al.* (2013) found that when gastrodin was co- administered with puerarin, both compounds showed higher bioavailability in the body and may be promising as a combined dose.

Hydroxybenzyl alcohol

Hydroxybenzyl alcohol is the metabolite product of gastrodin, and has been identified beside gastrodin as a pharmacologically active component in g. elata (Yu *et a*l., 2005).

HBA has been reported to have protective effects against brain injury caused by ischaemic stroke (Yu *et al*., 2005). It also inhibits DNA degradation, protects the brain after neurotoxic injury (Huh *et al.*, 1995; Hsieh *et al.*, 1997; Kim *et al*., 2003) and reduced brain lesion size (Yu *et al*., 2013). Besides itself exerting activity, HBA facilitates gastrodia interaction with receptors in the brain through binding with specific receptors (Guo *et al*., 1991). Interestingly, HBA has been mentioned in some studies as being more potent than its glycone gastrodin. In a study comparing gastrodin and HBA activity on learning and memory, Hsieh *et al.* (1997) report that HBA is the more potent constituent. While the mechanism for neuroprotection has not been elucidated, studies point towards the possible role of HBA as a putative antioxidant, preventing neuronal injury that mostly occurs due to oxidative stress (Yu *et al.*, 2013). A study has also reported that g. elata reduced lipid peroxide levels and exerts free radical- scavenging activities in seizure- induced rats (Liu and Mori, 1992, 1993) which may be attributed to vanillin and HBA. HBA is preserved in the brain, where it intermediates pharmacological activity in the CNS.

Conclusion

Chunma *(Gastrodia elata)*, a typical Korean plant, has been proven to contain various health-promoting agents, thus has very high potential to be developed into various end-products, including food supplement. This plant is seen to be as good as ginseng in the world market in the very near future.

References

An, S.J., Park, S.K., Hwang, I.K., Choi, S.Y., Kim, S.K., Kwon, O.S., Jung, S.J., Baek, N.I., Lee, H.Y., Won, M.H. and Kang, T.C. 2003. Gastrodin decreases immunoreactivities of γ-aminobutyric acid shunt enzymes in the hippocampus of seizure-sensitive gerbils. Journal of Neuroscience Research 71(4): 534-543.

Baek, N.I., Choi, S.Y., Park, J.K., Cho, S.W., Ahn, E.M., Jeon, S.G., Lee, B.R., Bahn, J.H., Kim, Y.K. and Shon, I.H. 1999. Isolation and identification of succinic semialdehyde dehydrogenase inhibitory compound from the rhizome of *Gastrodia elata* Blume. Archives of Pharmacal Research 22(2): 219-224.

Bai, Y., Yin, H., Bi, H., Zhuang, Y., Liu, T. and Ma, Y. 2016. De novo biosynthesis of Gastrodin in *Escherichia coli*. Metabolic Engineering 35: 138-147.

Beckman, J.S., and Crow, J.P. 1993. Pathological implications of nitric oxide, superoxide and peroxynitrite formation. Biochemical Society Transactions 21(2): 330-334.

Bensky, D., Clavey, S. and Stoger, E. 2004. (compiled and translated), Chinese Herbal Medicine Materia Medica, p. 970-973. Seattle, USA: Eastland Press.

Breton, C., Šnajdrová, L., Jeanneau, C., Koča, J. and Imberty, A. 2006. Structures and mechanisms of glycosyltransferases. Glycobiology 16(2): 29R-37R.

Chae, S.W., Lee, A., Lee, H.W., Yoon, T.S., Moon, B.C., Choo, B.K. and Kim, H.K. 2008. Three phenolic glycosides from *Gastrodia elata.* Journal of Applied Biological Chemistry 51(2): 61-65.

Chik, S.C., Or, T.C., Luo, D., Yang, C.L. and Lau, A.S. 2013. Pharmacological effects of active compounds on neurodegenerative disease with gastrodia and uncaria decoction, a commonly used poststroke decoction. The Scientific World Journal 2013.

Choi, S.I., Ju, W.K., Choi, E.K., Kim, J., Lea, H.Z., Carp, R.I., Wisniewski, H.M. and Kim, Y.S. (1998). Mitochondrial dysfunction induced by oxidative stress in the brains of hamsters infected with the 263 K scrapie agent. Acta Neuropathologica 96(3): 279-286.

Dai, J.N., Zong, Y., Zhong, L.M., Li, Y.M., Zhang, W., Bian, L.G., Ai, Q.L., Liu, Y.D., Sun, J. and Lu, D. 2011. Gastrodin inhibits expression of inducible NO synthase, cyclooxygenase-2 and proinflammatory cytokines in cultured LPS-stimulated microglia via MAPK pathways. PloS One 6(7): e21891.

Ducros, V.M., Tarling, C.A., Zechel, D.L., Brzozowski, A.M., Frandsen, T.P., von Ossowski, I., Schülein, M., Withers, S.G. and Davies, G.J. 2003. Anatomy of glycosynthesis: structure and kinetics of the *Humicola insolens* Cel7B E197A and E197S glycosynthase

mutants. Chemistry and Biology 10(7): 619-628.

Fan, L., Dong, Y., Xu, T., Zhang, H. and Chen, Q. 2013. Gastrodin production from p-2-hydroxybenzyl alcohol through biotransformation by cultured cells of *Aspergillus foetidus* and *Penicillium cyclopium*. Applied Biochemistry and Biotechnology 170(1): 138-148.

Guo, Z., Tan, T., Zhong, Y. and Wu, C. 1991. [Study of the mechanism of gastrodin and derivatives of gastrodigenin]. Journal of West China University of Medical Sciences 22(1): 79-82.

Ha, J.H., Lee, D.U., Lee, J.T., Kim, J.S., Yong, C.S., Kim, J.A. and Ha, J.S. 2000. 4-Hydroxybenzaldehyde from *Gastrodia elata* B1. is active in the antioxidation and GABAergic neuromodulation of the rat brain. Journal of Ethnopharmacology 73(1): 329-333.

Hayashi, J., Sekine, T., Deguchi, S., Lin, Q., Horie, S., Tsuchiya, S., Yano, S., Watanabe, K. and Ikegami, F. 2002. Phenolic compounds from *Gastrodia rhizome* and relaxant effects of related compounds on isolated smooth muscle preparation. Phytochemistry 59(5): 513-519.

Hsieh, C.L.,Chiang, S.Y., Cheng, K.S., Lin, Y.H., Tang, N.Y., Lee, C.J., Pon, C.Z. and Hsieh, C.T. 2001. Anticonvulsive and free radical scavenging activities of *Gastrodia elata* Bl. in kainic acid-treated rats. The American Journal of Chinese Medicine 29(2): 331-341.

Hsieh, M.T., Wu, C.R. and Chen, C.F. 1997. Gastrodin and p-hydroxybenzyl alcohol facilitate memory consolidation and retrieval, but not acquisition, on the passive avoidance task in rats. Journal of Ethnopharmacology 56(1): 45-54.

Huang, N.K., Lin, Y.L., Cheng, J.J. and Lai, W.L. 2004. Gastrodia elata prevents rat pheochromocytoma cells from serum-deprived apoptosis: the role of the MAPK family. Life Sciences 75(13): 1649-1657.

Huh, K., Yi, S.J., Shin, U.S. and Park, J.M. 1995. Effect of the ether fraction of *Gastrodia elata* methanol extract on the pentylenetetrazole-induced seizures. Journal of Applied Pharmcology 3: 199-204.

Jiang, G., Wu, H., Hu, Y., Li, J. and Li, Q. 2014. Gastrodin inhibits glutamate-induced apoptosis of PC12 cells via inhibition of CaMKII/ASK-1/p38 MAPK/p53 signaling cascade. Cellular and Molecular Neurobiology 34(4): 591-602.

Jiang, L., Dai, J., Huang, Z., Du, Q., Lin, J. and Wang, Y. 2013. Simultaneous determination of gastrodin and puerarin in rat plasma by HPLC and the application to their interaction on pharmacokinetics. Journal of Chromatography 915: 8-12.

Jie and Guo. 1984. Gastrodin chemical synthesis method suitable for industrialization. Patent Number: CN103275146 A. Retrieved from: *https://www.google.com/patents/CN103275146A?cl=en*

Jixun, Z., Hongzhu, G., Jungui, D., Yuanxing, Z. and Dean, G. 2001. Biotransformation of Gastrodin by *Mucor spinosus*. Journal of Chinese Pharmaceutical Sciences 10(4): 187-189.

Kim, H.J., Kwak, I.S., Lee, B.S., Oh, S.B., Lee, H.C., Lee, E. M., Lim, J.Y., Yun, Y.S. and Chung, B.W. 2005. Enhanced yield of extraction from *Gastrodia elata* Blume by ultrasonication and enzyme reaction. Natural Product Sciences 11(3): 123-126.

Kim, H.J., Lee, S.R., and Moon, K.D. 2003. Ether fraction of methanol extracts of *Gastrodia elata*, medicinal herb protects against neuronal cell damage after transient global ischemia in gerbils. Phytotherapy Research 17(8): 909-912.

Kumar, H., Kim, I.S., More, S.V., Kim, B.W., Bahk, Y.Y., and Choi, D.K. 2013. Gastrodin protects apoptotic dopaminergic neurons in a toxin-induced Parkinson's disease model. Evidence-Based Complementary and Alternative Medicine 2013.

Lee, K.H., CKD Pharmaceutical, Y., Kim, B.S., Choi, Y.H. and Kim, C.H. 2013. Sleep Inducing Effect of *Gastrodia elata* Fermented with Lactic Acid Bacteria. Korean Journal of Pharmacognosy 44(3): 281-285.

Lee, Y.S., Ha, Y.S., Yong, Y.S., Lee, Y.S., Huh, Y.S. and Kang, Y.S. 1999. Inhibitory effects of constituents of *Gastrodia elata* Bl. on glutamate-induced apoptosis in IMR-32 human neuroblastoma cells. Archives of Pharmacal Research 22(4): 404-409.

Li, C., Chen, X., Zhang, N., Song, Y. and Mu, Y. 2012. Gastrodin inhibits neuroinflammation in rotenone-induced Parkinson's disease model rats. Neural Regeneration Research 7(5): 325.

Li, H.X., Ding, M.Y. and Yu, J.Y. 2001. Simultaneous determination of p-hydroxybenzaldehyde, p-hydroxybenzylalcohol,4-(β-D-glucopyranosyloxy)-benzyl alcohol, and sugars in *Gastrodia elata* blume measured as their acetylated derivatives by GC-MS. Journal of Chromatographic Science 39(6): 251-254.

Li, H.X., Ding, M.Y., Lv, K., Wei, Y. and Yu, J.Y. 2001. Identification and determination of the active compounds in *Gastrodia elata* Blume by HPLC. Journal of Liquid Chromatography and Related Technologies 24(4): 579-588.

Li, L.L., Zhang, Z.R., Gong, T., He, L.L., and Deng, L. 2006. Simultaneous determination of Gastrodin and Ligustrazine hydrochloride in dog plasma by gradient high-performance liquid chromatography. Journal of Pharmaceutical and Biomedical Analysis 41(4): 1083-1087.

Li, Y. and Ma, C. 2014. Improved synthesis of gastrodin, a bioactive component of a traditional Chinese medicine. Journal of the Serbian Chemical Society 79(10): 1205-1212.

Li, Y. and Zhang, Z. 2015. Gastrodin improves cognitive dysfunction and decreases oxidative stress in vascular dementia rats induced by chronic ischemia. International Journal of Clinical and Experimental Pathology 8(11): 14099.

Lin, L.C., Chen, Y.F., Lee, W.C., Wu, Y.T. and Tsai, T.H. 2008. Pharmacokinetics of gastrodin and its metabolite p-hydroxybenzyl alcohol in rat blood, brain and bile by microdialysis coupled to LC–MS/MS. Journal of Pharmaceutical and Biomedical Analysis 48(3): 909-917.

Lin, L.C., Chen, Y.F., Tsai, T.R. and Tsai, T.H. 2007.

Analysis of brain distribution and biliary excretion of a nutrient supplement, gastrodin, in rat. Analytica Chimica Acta 590(2): 173-179.

Liu, J. and Mori, A. 1992. Antioxidant and free radical scavenging activities of *Gastrodia elata* Bl. and *Uncaria rhynchophylla* (Miq.) Jacks. Neuropharmacology 31(12): 1287-1298.

Liu, M.X., Li, Q.F., Liu, Q., Huang, Z.Q., and Qiu, F. 2009. Study on Extraction Technology, Structure and Free Radical Scavenging Activity of Polysaccharides from Gastrodia elata B1 [J]. Food Science 3: 005.

Liu, X.Q. 2002. The constituents of the aerial part of *Gastrodia elata* Blume. Natural Product Sciences 8(4): 137-140.

Lu, G.W., Zou, Y.J. and Mo, Q.Z. 1985. Kinetic aspects of absorption, distribution, metabolism and excretion of 3H-gastrodin in rats. Acta Pharmaceutica Sinica 3: 001.

Niu, Y.W., Li, H.J., Dong, Y.C., Xu, D.Q. and Chen, Q.H. 2016. Improved Gastrodin Production of Biotransformation Conditions by Cultured Cells *Armillaria luteo-virens* Sacc and the Anti-inflammatory Activity In Vivo. Medicinal Chemistry 2016.

Noda, N., Kobayashi, Y., Miyahara, K. and Fukahori, S. 1995. 2,4-Bis-(4-hydroxybenzyl)-phenol from Gastrodia elata. Phytochemistry 39: 1247-1248

Ong, E.S., Heng, M.Y., Tan, S.N., Yong, H., Wan, J., Koh, H., Teo, C.C. and Hew, C.S. 2007. Determination of gastrodin and vanillyl alcohol in *Gastrodia elata* Blume by pressurized liquid extraction at room temperature. Journal of Separation Science 30(13): 2130-2137.

Peng, C.X., Gong, J.S., Zhang, X.F., Zhang, M. and Zheng, S.Q. 2008. Production of gastrodin through biotransformation of p-hydroxybenzyl alcohol using hairy root cultures of *Datura tatula* L. African Journal of Biotechnology 7(3).

Peng, Z., Wang, S., Chen, G., Liu, R., Deng, J., Liu, J., Zhang, T., Tan, Q. and Hai, C. 2015. Gastrodin alleviates cerebral ischemic damage in mice by improving anti-oxidant and anti-inflammation activities and inhibiting apoptosis pathway. Neurochemical Research 40(4): 661-673.

Qiu, F., Liu, T.T., Qu, Z.W., Qiu, C.Y., Yang, Z. and Hu, W.P. 2014. Gastrodin inhibits the activity of acid-sensing ion channels in rat primary sensory neurons. European Journal of Pharmacology 731: 50-57.

Shu, C., Chen, C., Zhang, D. P., Guo, H., Zhou, H., Zong, J., Bian, Z., Dong, X., Dai, J., Zhang, Y. and Tang, Q. 2012. Gastrodin protects against cardiac hypertrophy and fibrosis. Molecular and Cellular Biochemistry 359(1-2): 9-16.

Simonian, N.A. and Coyle, J.T. 1996. Oxidative stress in neurodegenerative diseases. Annual Review of Pharmacology and Toxicology 36(1): 83-106.

Sun, W., Miao, B., Wang, X.C., Duan, J.H., Ye, X., Han, W.J., Wang, W.T., Luo, C. and Hu, S.J. 2012. Gastrodin inhibits allodynia and hyperalgesia in painful diabetic neuropathy rats by decreasing excitability of nociceptive primary sensory neurons. PLoS One 7(6): e39647.

Taguchi, H., Yosioka, L., Yamasaki, K. and Kim, I.H. 1981 Studies on the constituents of *Gastrodia elata* Blume. Chemical Pharmacy Bulletin 29: 55-62

Tang, W. and Eisenbrand, G. 1992 Chinese drugs of plant origin, chemistry, pharmacology, and use in traditional and modern medicine, p. 19-44. Berlin: Springer-Verlag

Wang, Q., Chen, G. and Zeng, S. 2007. Pharmacokinetics of Gastrodin in rat plasma and CSF after in and iv. International Journal of Pharmaceutics 341(1): 20-25.

Wang, X.L., Xing, G.H., Hong, B., Li, X.M., Zou, Y., Zhang, X.J. and Dong, M.X. 2014. Gastrodin prevents motor deficits and oxidative stress in the MPTP mouse model of Parkinson's disease: Involvement of ERK1/2–Nrf2 signaling pathway. Life Sciences 114(2): 77-85.

Wu, C.R., Hsieh, M.T., Huang, S.C., Peng, W.H., Chang, Y.S. and Chen, C.F. 1996. Effects of *Gastrodia elata* and its active constituents on scopolamine-induced amnesia in rats. Planta Medica 62(4): 317-321.

Xue, S.T., He, W.Y., Ma, L.L., Wang, H.Q., Wang, B., Zheng, G.H., Ji, X.Y., Zhang, T., Li, Y.H., Jiang, J.D. and Li, Z.R. 2013. Synthesis and anti-Influenza virus activities of a novel class of gastrodin derivatives. Molecules 18(4): 3789-3805.

Yang, W.E.I., Yu, D.M. and Xia, L.H. 2001. Determination of Gastrodin in *Gastrodia elata* Blume by HPLC with ELSD and DAD [J]. Chemical Research in Chinese Universities 4: 011.

Yang, P., Han, Y., Gui, L., Sun, J., Chen, Y.L., Song, R., Guo, J.Z., Xie, Y.N., Lu, D. and Sun, L. 2013. Gastrodin attenuation of the inflammatory response in H9c2 cardiomyocytes involves inhibition of NF-κB and MAPKs activation via the phosphatidylinositol 3-kinase signaling. Biochemical Pharmacology 85(8): 1124-1133.

Yong, W., Xing, T.R., Wang, S., Chen, L., Hu, P., Li, C.C., Wang, H.L., Wang, M., Chen, J.T. and Ruan, D.Y. 2009. Protective effects of gastrodin on lead-induced synaptic plasticity deficits in rat hippocampus. Planta Medica 75(10): 1112-1117.

You, J., Tan, T., Kuang, A., Zhong, Y. and He, S. 1994. [Biodistribution and metabolism of 3H-gastrodigenin and 3H-gastrodin in mice]. Journal of West China University of Medical Sciences 25(3): 325-328.

Yu, S.J., Kim, J.R., Lee, C.K., Han, J.E., Lee, J.H., Kim, H.S., Hong, J.H. and Kang, S.G. 2005. *Gastrodia elata* blume and an active component, p-hydroxybenzyl alcohol reduce focal ischemic brain injury through antioxidant related gene expressions. Biological and Pharmaceutical Bulletin 28(6): 1016-1020.

Yu, S., Zhao, J., Wang, X., Lei, S., Wu, X., Chen, Y., Wu, J. and Zhao, Y. 2013. 4-Hydroxybenzyl alcohol confers neuroprotection through up-regulation of antioxidant protein expression. Neurochemical Research 38(7): 1501-1516.

Zeng, X., Zhang, S., Zhang, L., Zhang, K. and Zheng, X. 2006. A study of the neuroprotective effect of the

phenolic glucoside gastrodin during cerebral ischemia in vivo and in vitro. Planta Medica 72(15): 1359-1365.

Zhang, H.F., He, G.Q., Liu, J., Ruan, H., Chen, Q.H., Zhang, Q., Wang, J-L. and Zhang, H.B. 2008. Production of gastrodin through biotransformation of p-2-hydroxybenzyl alcohol by cultured cells of *Armillaria luteo-virens* Sacc. Enzyme and Microbial Technology 43(1): 25-30.

Zhang, W., Sheng, Y.X. and Zhang, J.L. 2008. Determination and pharmacokinetics of gastrodin and p-hydroxybenzylalcohol after oral administration of *Gastrodia elata* Bl. extract in rats by high-performance liquid chromatography–electrospray ionization mass spectrometric method. Phytomedicine 15(10): 844-850.

Zhao, X., Zou, Y., Xu, H., Fan, L., Guo, H., Li, X., Li, G., Zhang, X. and Dong, M. 2012. Gastrodin protect primary cultured rat hippocampal neurons against amyloid-beta peptide-induced neurotoxicity via ERK1/2-Nrf2 pathway. Brain Research 1482: 13-21.

Zhao, Y., Cao, Q.E., Xiang, Y. and Hu, Z. 1999i. Identification and determination of active components in *Gastrodia elata* Bl. by capillary electrophoresis. Journal of Chromatography A 849(1): 277-283.

Zhou, J., Yang, Y.B. and Pu, X.Y. 1980. The phenolic compounds of fresh Gastrodia elata blume. Yunnan Zhi Wu Yan Jiu 2: 370-374.

Zhu, H., Dai, P., Zhang, W., Chen, E., Han, W., Chen, C. and Cui, Y. 2010. Enzymic synthesis of gastrodin through microbial transformation and purification of gastrodin biosynthesis enzyme. Biological and Pharmaceutical Bulletin 33(10):1680-1684.

Zhu, Y.L. 2006. Therapeutic Efficacy of Gastrodin on migraine. In Public Medical Forum Magazine. Vol. 10, p. 312-313.