



Gastrodiae Rhizoma (天麻 tiān má): a review of biological activity and antidepressant mechanisms

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Abstract

Gastrodiae Rhizoma, also called chì jiàn (赤箭), guǐ dū yóu (鬼督郵), or tiān má (天麻) in Chinese, is considered a top grade (上品 shàng pǐn) medicine described to enter liver channel (肝經 gān jīng) in classic literatures of traditional Chinese medicine and has been used for centuries. Many studies investigating its various bioactivities and active compounds have been conducted worldwide. This article reviews these biological activities and details the antidepressant pharmacology of Gastrodiae Rhizoma. Gastrodiae Rhizoma treatment exerts an effective inhibition of diverse diseases and disorders, including convulsion, oxidative stress, mental disorders, amnesia, cardio-cerebral-vascular diseases, and inflammation, among others. The antidepressant effect of Gastrodiae Rhizoma was evaluated in animal models and several mechanisms of activity were found, including the modulation and regulation of monoamine oxidase activity, monoamine concentration and turnover, antioxidant activity, GABAergic system induction, BDNF induction, neuroprotection and anti-inflammatory activity.

Key words: *Gastrodia elata* Bl., Gastrodiae Rhizoma, Bioactivity, Depressive disorder, Traditional Chinese medicine

Overview

Gastrodiae Rhizoma is the dried tuber of *Gastrodia elata* Bl. which belongs to the Orchidaceae family and is widely-used in many Asian countries, including Taiwan, Japan, Korea, India, China, and others, as a traditional medicine for the treatment of many diseases. However, *Gastrodia elata* Bl. is difficult to cultivate, it grows in the forest at 400-3200 meters above sea level in the temperate zone. It is a myco-heterophyte that has a symbiotic relationship with the fungus *Mycena osmundicola* for germination and *Armillaria mellea* for nutrition on rotten wood (Kim et al., 2006b; Sekizaki et al., 2008; Xu and Guo, 2000). In Chinese, Gastrodiae Rhizoma is known as chì jiàn (赤箭), guǐ dū yóu (鬼督郵), or tiān má (天麻).

The biological activity and the active compounds of Gastrodiae Rhizoma are popular study topics by

researchers worldwide, although most studies mainly come from Korea, Taiwan, Japan, and China. This article aims to review the biological activities and antidepressant pharmacology of Gastrodiae Rhizoma.

Traditional uses of Gastrodiae Rhizoma

Gastrodiae Rhizoma is recorded in many traditional Chinese medicine classics, including The Divine Husbandman's Herbal Foundation Canon (神農本草經 shén nóng běn cǎo jīng), Variorum of the Divine Husbandman's Herbal Foundation Canon (神農本草經集註 shén nóng běn cǎo jīng jí zhù), and the Herbal Foundation Compendium (本草綱目 běn cǎo gāng mù).

In The Divine Husbandman's Herbal Foundation Canon (神農本草經 shén nóng běn cǎo jīng), Gastrodiae Rhizoma (赤箭 chì jiàn, or 鬼督郵 guǐ dū yóu) is considered as a top grade (上品 shàng pǐn)

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drug, the medicine with rejuvenating effect, no toxic and can be long-term used without harm. The Divine Husbandman's Herbal Foundation Canon (神農本草經 shén nóng běn cǎo jīng), the Variorum of the Divine Husbandman's Herbal Foundation Canon (神農本草經集註 shén nóng běn cǎo jīng jí zhù), and the Newly Revised Herbal Foundation (新修本草 xīn xiū běn cǎo) all indicate that treatment with *Gastrodiae Rhizoma* (赤箭 chī jiàn) for a long period of time can boost qi and bodily strength (氣力 qì lì), increase yin (長陰 zhǎng yīn), enhance health (肥健 fèi jiàn), rejuvenate the body (輕身 qīng shēn), and extend life (增年 zēng nái).

In Herbal Foundation for Decoctions (湯液本草 tāng yè běn cǎo), *Gastrodiae Rhizoma* (天麻 tiān má) is used to treat head wind (頭風 tóu fēng; chronic headache with repeated recurrence), wind-damp impediment (風濕痺 fēng shī bì), hypertonicity of the limbs (四肢拘攣 sì zhī jū luán), and wind epilepsy (風癇 fēng xián) as well as fright qi (驚氣 jīng qì) in children. It is also good for the lumbus (腰 yāo), knee (膝 xī), and sinew force (筋力 jīn lì).

In the Compendium of Materia Medica (本草綱目 běn cǎo gāng mù shí yí), *Gastrodiae Rhizoma* (天麻 tiān má) is described as medicine improving liver channel (肝經 gān jīng) and qi aspect (氣分 qì fèn). The Essential Herbal Foundation (本草備藥 běn cǎo bèi yào) described *Gastrodiae Rhizoma* (天麻 tiān má) as a medicine that is warm and acrid (辛溫 xīn wēn) and that can dispel wind (祛風 qū fēng), enter liver channel (肝經 gān jīng), boost qi (益氣 yì qì), strengthen yin (強陰 qiáng yīn), free the blood vessels (通血脈 tōng xuè mài), strengthen sinew force (強筋力 qiáng jīn lì), and course phlegm qi (疏痰氣 shū tán qì). *Gastrodiae Rhizoma* is also used for the treatment of all wind with shaking and dizzy vision (諸風掉眩 zhū fēng diào xuàn), spinning head (頭旋 tóu xuàn), black rings around the eyes (眼黑 yǎn hēi), paralyzed speech (語言不遂 yǔ yán bù suì), and wind-damp impediment (風濕痺 fēng shī bì), as well as fright-epilepsy in infants (小兒驚癇 xiǎo ér jīng xián).

In summary, *Gastrodiae Rhizoma* is a top grade (上品 shàng pǐn) medicine that enters the liver channel (肝經 gān jīng) and is used to treat ailments such as headache, dizziness, convulsion, paralysis, rheumatism, and lumbago. Therefore, *Gastrodiae Rhizoma* enhances health and prolongs life according to the classics of traditional Chinese medicine.

Scientific evidence supporting the biological activities of *Gastrodiae Rhizoma*

Anticonvulsion

The effect of the methanol or water extract from *Gastrodiae Rhizoma* as well as its isolated active compounds, i.e., gastrodin, vanillyl alcohol, vanillin, S-(4-hydroxybenzyl)-glutathione, and p-hydroxybenzaldehyde, on anticonvulsive activity were all studied *in vitro* or *in vivo*. *Gastrodiae Rhizoma* extract or its active compounds significantly reduced the convulsive syndrome in rodents induced by kainic acid (Hsieh et al., 2001; Hsieh et al., 1999; Kim et al., 2001), ferric chloride (Hsieh et al., 2000a), or pentylenetetrazole (Ha et al., 2000), and decreased the seizure scores in seizure-sensitive gerbils (An et al., 2003). Kainic acid is a neurotoxic agent that acts by binding and activating glutamate receptors in the central nervous system to increase both oxidative stress and neuron damage; kainic acid can also induce activator protein 1 complex that may affect neuronal plasticity. S-(4-hydroxybenzyl)-glutathione inhibits the binding of kainic acid to the glutamate receptor in rats' neurons within the cerebral cortex (Andersson et al., 1995). *Gastrodiae Rhizoma* treatment also exhibited increased antioxidant activity, free radical scavenging, and neuron protection in damaged cells induced by kainic acid, ferric chloride, or glutamate (Ha et al., 2000; Hsieh et al., 2000a; Hsieh et al., 2005; Hsieh et al., 2001; Kim et al., 2001; Lee et al., 1999; Liu and Mori, 1992). *Gastrodiae Rhizoma* regulated activator protein 1 expression via the JNK signaling pathway in kainic acid-induced convulsion animal models (Hsieh et al., 2007). Other studies found that *Gastrodiae Rhizoma* decreases gamma-aminobutyric acid (GABA) shunt enzymes and increases GABA content in seizure-sensitive gerbils or in rats injected with pentylenetetrazole (An et al., 2003; Ha et al., 2000).

Antioxidation

The antioxidant activity of *Gastrodiae Rhizoma* was studied and the active compounds, including vanillyl alcohol, vanillin, and p-hydroxybenzyl alcohol, were found to scavenge free radicals (Hsieh et al., 2000a; Lee et al., 2006; Liu and Mori, 1993). The water and methanol extracts of *Gastrodiae Rhizoma* also inhibited lipid peroxidation induced by hydrogen peroxide, ferric chloride, and iron-ascorbate (Jung et al., 2007; Liu and Mori, 1992, 1993). These results indicate that *Gastrodiae Rhizoma* can be used as an effective antioxidant.

Treatment for mental disorder

The effect of *Gastrodiae Rhizoma* on mental disorders such as depression, anxiety, and schizophrenia has been investigated by animal models.

In both the forced-swimming test and tail-suspension test, animal models used for evaluation of antidepressant activity, the water and the ethanol extract of *Gastrodiae Rhizoma* demonstrated a significant antidepressant effect (Chen et al., 2008; Chen et al., 2009; Zhou et al., 2006). Both the serotonergic and the dopaminergic systems in the rats' brain were significantly increased by the water extract of *Gastrodiae Rhizoma*. In this model, the concentrations of serotonin and dopamine were elevated, while the turnover of these two monoamines was decreased after orally *Gastrodiae Rhizoma* treatment (Chen et al., 2009). Furthermore, the water extract of *Gastrodiae Rhizoma* attenuated memory impairment loss by the animals as measured by the inhibitory avoidance task and the Morris water maze in rats (Chen et al., 2011). This is a significant finding, as memory impairment is a common problem that affects patients with depression.

The water extract of *Gastrodiae Rhizoma*, containing the 4-hydroxybenzyl alcohol and 4-hydroxybenzaldehyde active compounds, showed anxiolytic effects in the elevated plus-maze test in mice. This study further showed that the anxiolytic effects of these compounds might involve the serotonergic or GABAergic system (Jung et al., 2006). Another active compound from *Gastrodiae Rhizoma*, parishin C, can ameliorate schizophrenia-like psychosis induced by phencyclidine, a non-competitive N-methyl-D-aspartate (NMDA) antagonist (Shin et al., 2010). Furthermore, the anti-psychotic effect of *Gastrodiae Rhizoma* may be due to its activation of the 5-HT receptor.

Neuroprotection

The neuroprotective activity of *Gastrodiae Rhizoma* was studied in different animal models and cell lines. The methanol or ethanol extracts of *Gastrodiae Rhizoma* as well as the pure compounds gastrodin and vanilli increased the cell viability of cell lines PC12 (rat pheochromocytoma cells), SH-SY5Y (human dopaminergic cells), or the primary neurons that underwent damage induced by serum deprivation, hypoxia, glutamate, hydrogen peroxide, potassium chloride, or 1-methyl-4-phenylpyridinium (An et al., 2010; Huang et al., 2007; Huang et al., 2004; Huang et al., 2006; Kam et al., 2011; Kim et al., 2007b; Xu et al., 2007; Zeng et al., 2006). Gastrodin also protected

neurons against lead-induced deficiencies in synaptic plasticity (Yong et al., 2009).

According to previous studies, treatment of the methanol extract of *Gastrodiae Rhizoma* or the pure compound vanillyl alcohol reduced oxidative stress and cell apoptosis in both SH-SY5Y and MN9D dopaminergic cell lines in response to the damage induced by the neurotoxin 1-methyl-4-phenylpyridinium (An et al., 2010; Kim et al., 2011), which normally induces a Parkinsonian-like syndrome *in vivo*. The neuroprotective effect of *Gastrodiae Rhizoma* in dopaminergic cells induced by 1-methyl-4-phenylpyridinium revealed that *Gastrodiae Rhizoma* might be an effective treatment for Parkinson's disease.

Amyloid β -peptide, an insoluble peptide found in the brains of patients with Alzheimer's disease, causes cell damage in both *in vitro* cell models and *in vivo* animal models. *Gastrodiae Rhizoma* methanol extract diminished damage induced by CT105, a carboxyl terminal fragment of amyloid β -protein precursor and amyloid β -peptide, in neuronal or neuron-like cells (Kim et al., 2007a; Kim et al., 2003; Kim et al., 2006a). In an animal model, *Gastrodiae Rhizoma* reversed learning and memory loss as well as a GABA imbalance induced by aluminum, a toxic metal related to neurodegenerative diseases such as Alzheimer's disease and Parkinsonian-induced dementia (Shuchang et al., 2008). These studies suggested that *Gastrodiae Rhizoma* may be a potential treatment for Alzheimer's disease.

Memory improvement

The effect of *Gastrodiae Rhizoma* on learning and memory function has been studied. In animal models, the water or methanol extract of *Gastrodiae Rhizoma* as well as the pure compounds gastrodin and *p*-hydroxybenzyl alcohol all confer protection from memory loss induced by drugs, including scopolamine (Hsieh et al., 2000b; Hsieh et al., 1997; Wu et al., 1996a; Wu et al., 1996b), cycloheximide (Hsieh et al., 1997; Wu et al., 1996b), apomorphine (Hsieh et al., 1997; Wu et al., 1996b), and aluminum chloride (Shuchang et al., 2008), or from stress induced using the forced-swimming process model (Chen et al., 2011). All learning and memory processes, including acquisition, consolidation, and retrieval, improved after *Gastrodiae Rhizoma* treatment in various animal models. The effect of *Gastrodiae Rhizoma* on serotonergic, dopaminergic, and GABAergic systems might explain how it can improve cognitive function.

Anti-cardio-cerebral-vascular diseases

The effect of the *Gastrodiae Rhizoma* compounds 4-hydroxybenzyl alcohol and gastrodin on the damage incurred on the cardio-cerebral-vascular system in the middle cerebral arterial occlusion (MCAO) animal model, commonly used to study ischemic stroke, was evaluated by several studies. These studies showed that 4-hydroxybenzyl alcohol and gastrodin significantly decreased the infarct and edema volume, and promoted functional recovery (Descamps et al., 2009; Kam et al., 2011; Yu et al., 2005; Yu et al., 2010; Zeng et al., 2006). *Gastrodiae Rhizoma* upregulated protein disulfide isomerase (PDI), 1-Cys peroxiredoxin (1-Cys Prx), and nuclear factor-E2-related factor 2 (Nrf2) genes; it also exerted neuroprotective and antioxidant effects (Descamps et al., 2009; Kam et al., 2011; Yu et al., 2005). The protective effects of 4-hydroxybenzyl alcohol against stroke can be attributed to its modulation of antiapoptotic activity and neurotrophic factors, including glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and myelin basic protein (MBP) (Kam et al., 2011; Yu et al., 2010). In a microdialysis study, gastrodin affected the concentration of glutamate and GABA in an MCAO model (Zeng et al., 2007). The neuroprotective effects of vanillin, 4-hydroxybenzyl alcohol, and 4-hydroxybenzaldehyde on the hippocampus have also been supported in a transient global ischemia model (Kim et al., 2007b).

Moreover, the phenolic compounds from *Gastrodiae Rhizoma* inhibited platelet aggregation induced by collagen, epinephrine, sodium arachidonate, and 9,11-dideoxy-11 α ,9 α -epoxymethanoprostagrandin F2 α (Pyo et al., 2004). In primary cultured human umbilical vein endothelial cells, pretreatment with *Gastrodiae Rhizoma* ethanol extract significantly decreased the tumor necrosis factor (TNF)- α -induced increase of matrix metalloproteinase (MMP)-2 and MMP-9, which play key roles in the development of atherosclerosis (Lee et al., 2009). These studies revealed that *Gastrodiae Rhizoma* might be a preventive or therapeutic drug for atherosclerosis and related ischemic stroke disease.

Gastrodiae Rhizoma is used for the treatment of hypertension, headache, migraine, dizziness, etc. The relaxant effects of the *Gastrodiae Rhizoma* water extract and phenolic compounds were demonstrated in several studies (Hayashi et al., 2002; Teong et al., 2011). The inhibition of smooth muscle contraction may provide evidence of *Gastrodiae Rhizoma*'s inhibitory effects on hypertension, headache, and related cardio-cerebral-

vascular diseases.

Anti-inflammation

The ethanol extract and the isolated phenolic compounds from *Gastrodiae Rhizoma*, including 4-hydroxybenzaldehyde, 4-hydroxybenzyl alcohol, benzyl alcohol, vanillyl alcohol, and vanillin, exhibited anti-inflammatory activity in carrageenan, acetic acid, or arachidonic acid-induced inflammation models, as well as analgesic activity in an acetic acid-induced writhing response (Ahn et al., 2007; Lee et al., 2006). The ethanol extract also demonstrated anti-angiogenic activity in chick embryo chorioallantoic membrane assay (Ahn et al., 2007). The anti-inflammatory activity of *Gastrodiae Rhizoma* is attributed to its inhibition of both cyclooxygenase (COX) activity and oxidative stress (Ahn et al., 2007; Hwang et al., 2009; Lee et al., 2006).

Other activities

Many other biological activities of *Gastrodiae Rhizoma* were studied. It was found to have anti-dengue virus (Qiu et al., 2007; Tong et al., 2010), anti-cancer (Heo et al., 2007), and anti-asthma activities (Jang et al., 2010). Additionally, it was shown to improve insulin resistance (Park et al., 2011) and inhibit DNA topoisomerase I and II activity (Lee et al., 2007), among other effects.

Antidepressant mechanisms of *Gastrodiae Rhizoma*

Depression is currently ranked among the top 3 high-burden diseases in the world and is predicted to be the world's number one by the year 2030 (Mathers et al., 2008). Although various antidepressants are commercially available, the accompanying side effects lead to poor therapeutic compliance (Demyttenaere, 2003). Therefore, we tried to find an alternative treatment for depression. *Gastrodiae Rhizoma* was demonstrated to exert an antidepressant effect in several animal models, including the forced-swimming test and the tail-suspension test (Chen et al., 2008; Chen et al., 2009; Zhou et al., 2006). However, the mechanism of antidepressant action of *Gastrodiae Rhizoma* has not been fully elucidated and more studies on these antidepressant mechanisms are needed. In this section, we review the possible antidepressant mechanisms of *Gastrodiae Rhizoma* based on previously published work.

Irregular monoamine neurotransmitter systems in the brain are considered one of the causes of depression

(Delgado, 2004; Hirschfeld, 2000; Kandel, 2000; O'Toole and Johnson, 1997; Thase, 2005). Previous studies indicated that the 3 key neurotransmitters, serotonin (5-HT), dopamine (DA), and norepinephrine (NE), are significantly lower in depressed patients' brains (Manji et al., 2001). Monoamine oxidase (MAO) enzymes, including MAO_A and MAO_B, modulate the metabolism of monoamines and therefore may be involved in diseases related to monoamines, such as depression (Du et al., 2002; Haier et al., 1988). Most of the currently used antidepressants target neurochemical functions. For example, fluoxetine, a common antidepressant used as a positive control in these studies, is one of the selective serotonin reuptake inhibitors (SSRI). Monoamine oxidase inhibitors could also improve depressive symptoms by modulating the metabolism of monoamines (Egashira et al., 1996; Gnerre et al., 2001; Holt and Baker, 1996). In our previous studies, we provided evidence that *Gastrodiae Rhizoma* had effects on monoamine modulation (Chen et al., 2008; Chen et al., 2009). We also found that *Gastrodiae Rhizoma* and its active components significantly decrease MAO_A and MAO_B activity *in vitro* (data unpublished).

Hydrogen peroxide is a by-product of monoamine oxidase enzyme activity. Hence, a monoamine oxidase inhibitor not only decreases the metabolism of monoamines but also reduces oxidative stress. Oxidative stress is implicated in many diseases, including depression (Bilici et al., 2001; Herken et al., 2001; Ravikumar et al., 2000; Yao et al., 2001). Superoxide dismutase (SOD) and malondialdehyde, the product of lipid peroxidation, are increased in the serum of depressed patients (Bilici et al., 2001; Khanzode et al., 2003). *Gastrodiae Rhizoma* and its active compounds demonstrate antioxidant activity in both *in vitro* and *in vivo* studies; they scavenge free radicals and inhibit lipid peroxidation (Hsieh et al., 2000a; Jung et al., 2007; Lee et al., 2006; Liu and Mori, 1992, 1993). Besides depression, the antioxidant system also has a role in cognitive function (Haque et al., 2008; Haque et al., 2006; Ouyang et al., 2005; Small, 1998) and memory loss, which are common symptoms in depressed patients. A role for *Gastrodiae Rhizoma* in improving learning and memory function has also been found (Chen et al., 2011). Therefore, the antioxidant activity of *Gastrodiae Rhizoma* may be one of the possible mechanisms that lead to the antidepressant activity and improvement in depression-related memory loss.

The dysfunctions of hypothalamic-pituitary-adrenal

axis (HPA axis) and glucocorticoids are observed in depressed patients (Jurueña et al., 2006; Marques et al., 2009; Pariante, 2009; Pariante and Lightman, 2008). The glucocorticoid receptors are mainly located in the hippocampus of the brain. Imbalanced glucocorticoids induced by an abnormal HPA axis cause neurotoxicity, neuron apoptosis, neuron decrease, loss of synapses, dendritic length decrease, and hippocampal volume reduction among other effects, and are related to depression (Sapolsky, 2000; Saylam et al., 2006; Shelton et al., 1999; Tata and Anderson, 2010; Tata et al., 2006). Therefore, glucocorticoids are used in both *in vitro* and *in vivo* experimental models as a neurotoxin to induce a depressive-like state (Huang et al., 2009; Johnson et al., 2006; Li et al., 2004). Antidepressants such as fluoxetine and desipramine exert neuroprotective effects by protecting cells against damage induced by dexamethasone, 5,7-dihydroxytryptamine, hydrogen peroxide, and corticosterone (Haynes et al., 2004; Kolla et al., 2005; Zhang et al., 1999; Zhu et al., 2006). Similarly, *Gastrodiae Rhizoma* also demonstrates neuroprotective and antiapoptotic effects in various animal or cell models (Hsieh et al., 2005; Huang et al., 2007; Huang et al., 2004; Kim et al., 2006a; Lee et al., 1999; Yu et al., 2010).

Stress induces hyperactivity of the HPA axis and regulates the concentration of brain-derived neurotrophic factor (BDNF) (Givalois et al., 2001; Kunugi et al., 2010; Li et al., 2009; Marmigère et al., 2003; Naert et al., 2011; Rage et al., 2002; Shelton, 2007), a protective neurotrophin which is highly expressed in hippocampus and hypothalamus of the brain (Tapia-Arancibia et al., 2004; Yan et al., 1997). BDNF is confirmed to be involved with depression (Aydemir et al., 2005), as it is decreased in depressed patients (Karege et al., 2002) and is elevated upon treatment with antidepressants (Aydemir et al., 2005; Dias et al., 2003; Hashimoto et al., 2004). Therefore, elevation of BDNF might be one of the antidepressant mechanisms used by *Gastrodiae Rhizoma*, as it has been shown to increase the expression of BDNF genes in an animal model (Kam et al., 2011).

γ -Aminobutyric acid (GABA) is an amino acid neurotransmitter in the central nervous system that interacts with monoamines in the brain (Petty, 1995) and exerts an anti-stress effect in humans (Vaiva et al., 2004). It is also involved in depression (Luscher et al., 2011) because GABA levels are significantly lower in depressed patients (Gerner and Hare, 1981; Honig et al., 1988; Luscher et al., 2011). Deficits in GABAergic

activity could induce depression-like effects in animal models (Earnheart et al., 2007; Shen et al., 2010). Antidepressants can also improve depression symptoms via GABAergic system regulation (Küçükbrahimoğlu et al., 2009). Similarly, several studies found that *Gastrodiae Rhizoma* could regulate GABA content or GABA metabolism (An et al., 2003; Baek et al., 1999; Choi and Lee, 2006; Ha et al., 2000; Ha et al., 2001; Kim et al., 2007b; Shuchang et al., 2008; Zeng et al., 2007) and might also interact with the GABA receptor itself (Jung et al., 2006). Therefore, *Gastrodiae Rhizoma* may mediate its antidepressant effect via GABA modulation.

Inflammatory markers, including c-reactive protein, interleukin-1, and interleukin-6 are positively associated with depression (Howren et al., 2009). A correlation between inflammatory markers and depression symptoms has also been found (Motivala et al., 2005; Reichenberg et al., 2001). These cytokines mediate many neural functions associated with depression, such as monoamine metabolism, neuroendocrine function, neural plasticity, neurotrophin production, and neural damage (McNally et al., 2008; Miller et al., 2009). COX-2 inhibitors have beneficial effects on depression (Müller and Schwarz, 2008) and antidepressants downregulate the inflammatory response (Kenis and Maes, 2002; Pollak and Yirmiya, 2002; Yaron et al., 1999). Studying the anti-inflammatory effect of *Gastrodiae Rhizoma* revealed that *Gastrodiae Rhizoma* decreases the induction of inflammatory cytokines, COX-2, and oxidative stress (Ahn et al., 2007; Hwang et al., 2009; Lee et al., 2006). This anti-inflammatory effect of *Gastrodiae Rhizoma* could also contribute to its antidepressant activity.

Overall, the antidepressant effect of *Gastrodiae Rhizoma* has been supported by various animal studies. However, the mechanisms behind its antidepressant activity need further investigation. This section reviewed the published studies and tried to elucidate the possible antidepressant mechanisms mediated by *Gastrodiae Rhizoma*. In animal models of depression, studies suggest that *Gastrodiae Rhizoma* mediates its antidepressant activity by modulating monoamine oxidase enzyme activity as well as monoamine concentration and turnover. Indirect evidence showed that antioxidant activity, GABAergic regulation, BDNF modulation, neuroprotection, and anti-inflammatory effects might also contribute to the antidepressant effect of *Gastrodiae Rhizoma*.

Conclusion

In summary, *Gastrodiae Rhizoma* is a traditional herb that possesses many biological activities and can act as an anticonvulsive, antioxidant, and antidepressant. The antidepressant effect of *Gastrodiae Rhizoma* has been demonstrated in various animal models; its antidepressant activity may be related to its ability to modulate monoamines as well as its antioxidant activity, GABAergic regulation, BDNF modulation, neuroprotection, and anti-inflammatory activity.

Although *Gastrodiae Rhizoma* is considered as a top grade (上品 *shàng pǐn*) medicine in ancient traditional medicine books, rigorous safety studies should be scientifically performed. More extensive clinical research, especially using randomized double-blind placebo-controlled crossover studies, is needed even though *Gastrodia Rhizoma* has been used for centuries and is regarded as an effective treatment for many diseases or symptoms of diseases. Furthermore, the biological activity of the active compound(s) need to be confirmed by further studies. More investigation is also needed to confirm and provide direct evidence for *Gastrodiae Rhizoma*'s antidepressant mechanisms.

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