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Review

Review on the characteristics of liver-pacifying medicinal in relation to the treatment of stroke: from scientific evidence to traditional medical theory☆

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ABSTRACT

Objective: To analyze the characteristics of liver pacifying medicinal in the treatment of brain disease to provide scientific evidence in clinical usage on stroke.
Methods: MEDLINE/PubMed, Google Scholar, and China National Knowledge Infrastructure Database were used as the literature sources. The Scientific name, Latin pharmaceutical name, Chinese name of 7 kinds of liver pacifying medicinal including Gouteng (*Ramulus Uncariae Rhynchophyllae cum Uncis*), Tianma (*Rhizoma Gastrodiae*), Juemingzi (*Semen Cassiae Obtusifoliae*), Quanxie (*Scorpio*), Wugong (*Scolopendra*), Jiangcan (*Bombyx Batryticatus*), and Dilong (*Pheretima Aspergillum*) were used as the keywords to search the databases for relevant publications up to July 2016. Their major compounds were also used as the keywords. The papers were selected based on the pharmacological activities and mechanisms of action related to brain diseases and subsequently, were analyzed and reviewed. We first described the origin, efficacy, and clinical indications of selected medicines, then brain disease specific activities focusing on stroke after the description of the general pharmacological activities.
Results: On the basis of the literature of scientific studies and clinical use in traditional medicine, we found and discussed the characteristics of liver pacifying medicinal in stroke treatment. First, liver-pacifying medicinal, or their components, might pass through the blood-brain barrier and act directly on neurons or on the neural network to provide protective effects against brain disease. Second, although it could be used throughout the disease duration, treatment of stroke might be more effective from the subacute up to the convalescent phase than the acute phase.
Conclusion: We can suggest that live pacifying medicinal has beneficial pharmacological activities directly or indirectly on neurons in brain disease and is useful for the treatment of stroke from subacute to convalescent phase.

Introduction

In Korean and Chinese traditional medicine, heat-clearing, liver-pacifying, and blood-activating stasis-dispelling medicinals have been considered as major therapeutic options for treating stroke patients [1–3]. Recently, we reviewed scientific researches and analyzed the characteristics of each medicinal to provide scientific evidence to their traditional usage on stroke. Among these medicinals, we previously reviewed the characteristics of blood-activating

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stasis-dispelling medicinal as stroke therapies based on scientific evidence and traditional medical theory [1]. In the current review, we further reviewed liver-pacifying medicinal and described the correlation between scientific reports and traditional medical theory.

Liver-pacifying medicinal have been used to treat wind syndromes, which are classified as external or internal. The external type of wind syndromes are characterized by fever, aversion to cold, sweating, floating, and tight pulse which can be treated with exterior-releasing medicinals, whereas the internal type syndromes are characterized by headache, vertigo, digestive disorders, sleep disorders, musculoskeletal paralysis, pruritus, tremor, abnormal relaxation of muscles, numbness, and spasm which can be treated with liver-pacifying medicinal [4,5]. The internal type of wind syndrome could be classified as central nervous system (CNS)-related or peripheral nervous system-related [4–6]. CNS-related wind syndrome derived from brain disease is considered as more severe and fatal than peripheral nervous system-related wind syndrome. For example, stroke caused by rupture (hemorrhage) or occlusion (ischemia) of the cerebral vessel could be considered a CNS-related syndrome [4,7–9]. Many attempts have been made to identify and demonstrate the activities of the active compounds of liver-pacifying medicinal on stroke [1,8,9].

Despite some differences between the liver-pacifying medicinal used in traditional medicine clinics in Korea and China, the following are considered the most important and frequently used: Lingyangjiao (*Cornu Saigae Tataricae*), Gouteng (*Ramulus Uncariae Rhynchophyllae cum Uncis*) (RURU), Tianma (*Rhizoma Gastrodiae*) (RG), Juemingzi (*Semen Cassiae Obtusifoliae*) (SCO), Quanxie (*Scorpio*), Wugong (*Scolopendra*), Jiangcan (*Bombyx Batryticatus*) (BB), Dilong (*Pheretima Aspergillum*), Shijueming (*Haliotidis Concha*), and Muli (*Ostreae Concha*). Of these, RURU, RG, and SCO possibly represent the most frequently used liver-pacifying medicinal in traditional medicine clinics [3,10–14]. Many studies have focused on the isolation of their active compounds and their efficacy in the treatment of brain disease [12,15–17]. Other medicines from animal source including Quanxie (*Scorpio*), Wugong (*Scolopendra*), BB, and Dilong (*Pheretima Aspergillum*) also have been regarded as important medicines in clinics for treating wind syndromes [3,13].

We reviewed the available pharmacological and pharmaceutical reports on RG, RURU, SCO, Quanxie (*Scorpio*), Wugong (*Scolopendra*), BB, and Dilong (*Pheretima Aspergillum)* and discussed their characteristics in relation to the treatment of brain diseases; in addition, we made recommendations for future studies on the basis of scientific evidence and traditional medical theory. The search terms were in accordance with the World Health Organization's international standard terminology for traditional medicine [18].

Methods

MEDLINE/PubMed, Google Scholar, and China National Knowledge Infrastructure Database (CNKI) were used as the literature sources. The Scientific name, Latin pharmaceutical name, Chinese name (in CNKI) of selected medicines and their major compounds were used as the keywords to search the databases for relevant publications up to July 2016. The papers were selected based on the pharmacological activities and mechanisms of action related to brain diseases focusing on stroke and subsequently, were analyzed and reviewed. For each medicine, we described the clinical use, general pharmacological activities, brain disease-specific activities focusing on stroke. Next, we discussed the characteristics of liver pacifying medicinal in stroke treatment.

Results

RG

RG, a tuber of *Gastrodia elata* Blume and a representative liver-pacifying medicinal, has been used to treat infantile convulsion, spasm, tetanus, dizziness, headache, hemiplegia, and limb numbness based on the effects of pacifying the liver to extinguish wind or arrest convulsions [3,5]. The indications for RG in traditional medicine are similar to those for CNS-related disease or CNS disease-related symptoms. Until recently, much research on RG has been conducted to demonstrate its pharmacological activities on CNS disease or related symptoms. Various effects of RG on vascular, nervous, and endocrine systems have been reported, including anti-inflammatory [19], hypotensive [20], hypocholesterolemic [20], anti-obesity [21], and anti-depressant [22] effects. In the field of brain diseases, RG has been extensively studied in neurodegenerative diseases such as Parkinson disease (PD), Alzheimer disease (AD), and stroke. In PD, an ethanol extract of RG and its components, gastrodin and vanillyl alcohol, are reported to protect against 1-methyl-4-phenylpyridinium–induced cell damage [23–26]. The extract of RG attenuated methamphetamine-induced behavioral and dopaminergic impairment [27] and alleviated L-dopa–induced dyskinesia in a 6-hydroxydopamine (6-OHDA)-induced PD model in mice [28]. A major compound, gastrodin, also showed protective effects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neuronal damage in mice [25,29]. The mechanisms involved anti-oxidative effects via the ERK1/2-nuclear factor erythroid 2-related factor 2 (Nrf2) signaling-related increase of hemeoxygenase 1, superoxide dismutase (SOD), and glutathione [23–25,29] and anti-apoptotic effects including the Bax/Bcl-2 mRNA, caspase-3, and cleaved poly (ADP-ribose) polymerase regulation [25]. In AD, a RG extract protected against cell damage from various inducers, including amyloid beta (Aβ) [30] and amyloid precursor protein [31,32]. It also protected *Drosophila* against Aβ–induced neurotoxicity [32]. The water extract of RG improved spatial memory with the reduction in number of amyloid deposits in the hippocampus of an Aβ 25–35–induced AD rat model[33], modulated amyloid precursor protein cleavage and cognitive function in mice [34], and attenuated learning deficits induced by forced-swimming stress [35]. It also improved learning and memory function, and normalized gamma-aminobutyric acid (GABA) levels in rats with aluminum chloride–induced learning and memory deficits [36]. Compounds of RG enhanced memory function and neuropathological changes in an Aβ 25–35–induced mouse AD model and a genetic mouse model, respectively [37,38], and in a scopolamine-induced amnesia mouse model [39]. One fractionation study revealed that all fractions showed protective effects against Aβ-induced cell death and the ethyl ether fraction was most effective [40]. In general, the mechanisms for the protective effects have been reported to be the inhibition of glial activation, anti-amyloidogenic effects [38], anti-apoptotic effects, and enhancing effects on anti-oxidative enzymes including SOD [32]. The mechanisms responsible for the memory-enhancing effects could be the maintenance of acetylcholine levels *via* increasing choline acetyltransferase and decreasing acetylcholinesterase (AChE) levels [33]. In the field of stroke, extracts of RG have shown protective effects against hippocampal damage in gerbils with global cerebral ischemia [41] and against transient middle cerebral artery occlusion (MCAo) in a rat model [42]. Compounds of RG have been studied more extensively than the extracts. Gastrodin protected against oxygen-glucose deprivation–induced cell death [43,44], reduced brain infarct and edema, and promoted functional recovery in a rat model with permanent MCAo [43]. One study that evaluated the effects of combination therapy with a polysaccharide of RG and electro-

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