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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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.

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.
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.

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Keywords: Stroke; Traditional medicine; Calming liver wind; Review

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. 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 stasis-dispelling medicinal as stroke therapies based on scientific evidence and traditional medical theory. 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, numbness, and spasm which can be treated with liver-pacifying medicinal. The internal type of wind syndrome could be classified as central nervous system (CNS)-related peripheral nervous system-related. 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. Many attempts have been made to identify and demonstrate the activities of the active compounds of liver-pacifying medicinal on CNS-related syndrome.

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 Asaiae Tataricae), Gouteng (Ramulus Uncariae Rhynchophyllae cum Unci) (RURU), Tianma (Rhizoma Gastrodiae) (RG), Juemingzi (Semen Cassiae Obovatae) (SCO), Quanxie (Scorpio), Wuqong (Scolopendra), Jiangle (Bombyx Batryticatus) (BB), Dilong (Pholidota Aspergillum), Shijueming (Halotidis Concha), and Muli (Ostreae Concha). Of these, RURU, RG, and SCO possibly represent the most frequently used liver-pacifying medicinal in traditional medicine clinics. Many studies have focused on the isolation of their active compounds and their efficacy in the treatment of brain disease. Other medicines from animal source including Quanxie (Scorpio), Wuqong (Scolopendra), BB, and Dilong (Pholidota Aspergillum) also have been regarded as important medicines in clinics for treating wind syndromes. We reviewed the available pharmacological and pharmaceutical reports on RG, RURU, SCO, Quanxie (Scorpio), Wuqong (Scolopendra), BB, and Dilong (Pholidota 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.

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. 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, hypotensive, hypocholesterolemic, anti-obesity, and anti-depressant 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. The extract of RG attenuated methamphetamine-induced behavioral and dopaminergic impairment and alleviated L-dopa-induced dyskinesia in a 6-hydroxydopamine (6-OHDA)-induced PD model in mice. 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. The mechanisms involved anti-oxidative effects via the ERK1/2-nuclear factor erythroid 2-related factor 2 (Nrf2) signaling-related increase of homeoxygenase 1, superoxide dismutase (SOD), and glutathione and anti-apoptotic effects including the Bax/Bcl-2 mRNA, caspase-3, and cleaved poly (ADP-ribose) polymerase regulation. In AD, a RG extract protected against cell damage from various inducers, including amyloid beta (Aβ) and amyloid precursor protein. It also protected Drosophila against Aβ-induced neurotoxicity. 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, modulated amyloid precursor protein cleavage and cognitive function in mice, and attenuated learning deficits induced by forced-swimming stress. It also improved learning and memory function, and normalized gamma-aminobutyric acid (GABA) levels in rats with aluminum chloride-induced learning and memory deficits. Compounds of RG enhanced memory function and neuropathological changes in an Aβ 25-35-induced mouse AD model and a genetic mouse model, respectively, and in a scopalamine-induced amnesia mouse model. One fractionation study revealed that all fractions showed protective effects against Aβ-induced cell death and the ethyl ether fraction was most effective. In general, the mechanisms for the protective effects have been reported to be the inhibition of glial activation, anti-amyloidogenic effects, anti-apoptotic effects, and enhancing effects on anti-oxidative enzymes including SOD. The mechanisms responsible for the memory-enhancing effects could be the maintenance of acetylcholine levels via increasing choline acetyl- transferase and decreasing acetylcholinesterase (AChE) levels. In the field of stroke, extracts of RG have shown protective effects against hippocampal damage in gerbils with global cerebral ischemia and against transient middle cerebral artery occlusion (MCAo) in a rat model. Compounds of RG have been studied more extensively than the extracts. Gastrodin protected against oxygen-glucose deprivation-induced cell death, reduced brain infarct and edema, and promoted functional recovery in a rat model with permanent MCAo. One study that evaluated the effects of combination therapy with a polysaccharide of RG and electro-acupuncture on focal cerebral ischemia in rat model revealed that 2 weeks of treatment protected against brain damage via upregulation in the expression of nestin and stem cell factor in the hippocampus. Extensively studied constituent compounds of RG include vanillin, 4-hydroxybenzyl aldehyde, 4-hydroxybenzyl alcohol, p-hydroxybenzyl alcohol, and gastrodin. p-hydroxybenzyl alcohol has been shown to protect against MCAo-induced brain injury, improve behavioral impairment, and protect against brain damage, even in ovariectomized female rats. 4-Hydroxybenzyl alcohol protected against MCAo-induced brain damage and against neuronal damage in a rat model of global cerebral ischemia. Vanillin prevented hippocampal CA1 cell death following global ischemia and hydroxyl-radical-induced PC12 cell damage. Possible mechanisms responsible for the protective effects of RG and its components include the inhibition of Ca2+ and nitric oxide increases; inhibition of glutamate levels; anti-oxidation; increases in GABA levels; regulation of Nrf2, protein disulfide isomerase, and neurotrophic factor genes; induction of protein disulfide isomerase in brain; and regulation of apoptotic factors, including Bcl-2 and caspase-3. RG and its components have various other activities, including anti-depressive effects via activating dopaminergic and serotonergic nervous system, anti-atherosclerotic effects via decreases in tumor necrosis factor a-induced increases in matrix metalloproteinase (MMP)-2/MMP-9 activities, hypotensive effects in spontaneously hypertensive rats fed a high-fat diet, and anti-inflammatory effects in human umbilical vein endothelial cells and RAW264.7 macrophages.

RURU

RURU is a hook-bearing branch of several Uncaria species. The original plants are slightly different between Korea, China, and Japan. Uncaria sinensis (US) and closely related plants of the same genus have been used in Korea. Uncaria rynchophylla (UR) and Uncaria macrophylla (UM) are used in Japan, and young branches with horns of US, UR, UM, Uncaria hirsute (UH), and Uncaria sessilifructus (USS) are used in China. RURU could also be considered a representative of liver-pacifying medicinal along with RG. It has been used clinically for the treatment of headache, vertigo, fright epilepsy with convulsions, eclampsia of pregnancy, and hypertension with the effects of extinguishing wind to arrest convulsions and clearing heat to pacify the liver. Although RURU comprises several species, we used the drug name...
“RURU” in the current review for the reader’s convenience and improved understanding. The indications for RURU are very similar to those for RG. However, RURU has typically been used to treat the symptoms related to the convulsive state, including hypertension, epilepsy, and spasm.3,4 To date, studies on RURU have been conducted to demonstrate the pharmacological activities focusing on CNS, especially on epilepsy or spasm. In recent years, the bioactivity and effects of RURU extracts and its major components i.e., rhynchophylline or its derivatives, have been increasingly investigated. These include anticonvulsive,7 anti-inflammatory,66 anti-oxidant,61 cytoprotective,62 hypotensive,69 and immunoregulatory83 effects. In the field of brain diseases, RURU has been extensively studied for its effects on epilepsy and neurodegenerative diseases, but there are relatively few reports about its protective effects against cerebral ischemia. The alkaloid components of RURU, including rhynchophylline and its derivatives, are possibly the primary compounds responsible for its effects, especially on brain diseases. RURU and its compounds have shown anticonvulsive effects in rats with kainic acid-induced epileptic seizures via Toll-like receptors, neurotrophin-signaling pathways, brain-derived neurotrophic factors (BDNF), and c-Jun N-terminal kinase signaling pathways (via inhibition of neuronal death),83 as well as astrogliosis,66 anti-inflammatory effect,67 and anti-oxidative effects.66,68 Various extracts of RURU or its components inhibited Aβ-induced cell damage and aggregation and destabilized preformed Aβ fibrils.67,70 One bioassay-guided isolation study revealed that rhynchophylline and isorhynchophylline were the major active compounds responsible for the protective effects against Aβ-induced neuronal death, which might be mediated via the inhibition of intracellular calcium overloading and tau protein hyper-phosphorylation.71 RURU and its components (alkaloids) have been shown to restore memory function in various chemical-induced amnesia models, including d-galactose,72 ibotenic acid,73 and scopolamine.74 The pharmacological activities of RURU on stroke have also been investigated. Total alkaloids,75 hexane and methanol extracts,76 and water extracts77 of RURU have been shown to attenuate focal and global cerebral ischemia-derived brain damage, edema, neuronal apoptosis, and neurological functions. The action mechanisms include anti-oxidative effects,73 enhancing effects on endothelial nitric oxide synthase,63 anti-inflammatory effects,77 and anti-N-methyl-D-aspartate effects.80 In addition to its protective effects against brain diseases, RURU and its components also have various effects on the vascular system. These include vasodilatory effects via both Ca²⁺-dependent81,82 and endothelium-derived relaxing factor/nitric oxide pathways,83 angiogenic effects via increases in vascular endothelial growth factor (VEGF) gene expression,84 inhibitory effects on MMP-2 and MMP-9,85 anti-oxidative effects,81,82 and anti-inflammatory effects via inhibition of nitric oxide, prostaglandin E2, inducible nitric oxide synthase, cyclooxygenase-2, and interleukin 1β.81,82-84

**SCO**

SCO, a seed of Cassia tora L. and C. obtusifolia L. and a representative liver-pacifying medicinal, has been used to treat painful red eye, photophobia with dacyrorhrea, bluish blindness, night blindness, headache, dizziness, dim vision, dysuria, ascites due to liver cirrhosis, and constipation based on the effects of clearing the liver and improving vision or draining water and relaxing the bowels.53 Various effects of SCO on ophthalmic, hepatic, vascular, nervous, and endocrine systems have been reported, including anti-oxidative, inflammatory, anti-diabetic, hypotensive, hepatoprotective, hypocholesterolemic, anti-obesity, anti-cancer and anti-cataract effects.99-101 In the field of brain diseases, SCO has been studied in neurodegenerative diseases such as PD, AD, and stroke. In PD, ethanol extract of Cassia obtusifolia (ECO, 50 mg/kg, 15 d) significantly protected neurons in substantia nigra and striatum MPTP-induced PD mouse model and also attenuated the PC12 cell damage induced by 6-OHDA.102 In AD, ECO ameliorated Aβ-induced synaptic dysfunction in hippocampal slice culture by inhibiting GSK-3β and it (50 mg/kg, 15 d) also protected against Aβ-induced memory impairment and inhibited inducible nitric oxide synthase and cyclooxygenase expressions in mice.103 Oral administration of ECO (25, 50, or 100 mg/kg) attenuated scopolamine-induced cognitive impairments in passive avoidance, Y-maze and Morris water maze test.104 In case of stroke, ECO attenuated neuronal damage in hippocampus via upregulation of BDNF expression and cAMP response element-binding protein (CREB) phosphorylation in CA1 of 2-vessel occlusion (VO) induced transient global cerebral hypoxia-ischemia mouse model.104 It also attenuates cognitive memory function investigated by in passive avoidance, Y-maze and Morris water maze tests in 2-VO mouse model and showed the inhibitory effects on AChE in *in vitro* and *ex vivo* study.105 Pre- (5 d before MCAo) and post-administration (4 weeks after MCAo) of the prescription containing 7 herbs including SCO (1.1-5.5 g/kg) showed protective effects on brain damage, neurologic score in transient MCAo rat model via the mechanisms related to N-methyl-d-aspartate receptor and ERK-CREB pathway.105 Another prescription, Daming capsule administration for 30 d (100 and 200 mg/kg) also showed the attenuation in neuronal death, cognitive and memory dysfunction in chronic 2-VO rat model.106 The chemical compounds of SCO also showed neuroprotective activities in various brain diseases. Briefly, emodin, emodin-8-O-β-D-glucoside and chrysophanol, well-known anthraquinone
derivatives of several traditional medicines including Rheum species and SCO have been well documented the neuroprotective effects on AD and stroke. Cassiaside, a naphthopyrone glucoside of C. obtusifolia was reported to inhibit AChE, butryrylcholineesterase, and β-site amyloid precursor protein cleaving enzyme 1 enzyme which are known to be major pathologic factors in AD. Intra-peritoneal injection of obtusifolin (0.5 mg/kg) and its derivative gluco-obtusifolin (2 mg/kg) isolated from SCO were reported to ameliorate cognitive-memory function which might be related to AChE production and activity. 

**Quanxie (Scorpio)**

Quanxie (Scorpio) is a dried body of Buthus martensii Karsch. It has been used clinically for the treatment of internal wind syndrome with convulsion including deviated eye and mouth, convulsion, hemiplegia, tetanus, insensitivity, and headache. To date, inhibitory effects of Quanxie (Scorpio) extracts or peptide on platelet aggregation have been considered as one of its major activities and are somewhat well-documented. Briefly, Quanxie (Scorpio) inhibited the formulation of the thrombus through the mechanism of improving fibrinogen lysis and inhibiting platelet aggregation in animal models. In the field of brain disease, anti-epileptic effects of Quanxie (Scorpio) extracts or venom peptides have been well-investigated and documented. The prescriptions containing Quanxie (Scorpio) inhibited convulsion induced by various chemicals including pentyleneterazol, kainic acid, penicillin, and lithium-pilocarpine by the mechanisms of enhancing GABA production and inhibiting c-fos, proenkephalin expression and also protected neurons against the damage in kainic acid, lithium-pilocarpine induced epilepsy animal models. The prescription containing Quanxie (Scorpio) also inhibited the epileptic seizure in rats, mice, and dogs.

In addition, Scorpion venom heat-resistant peptide enhanced neurogenesis and neurite outgrowth of immature neurons in adult mice by up-regulating BDNF, which is an important part of the brain recovery process in brain disease or injury. In addition, it was protective against Aβ-toxicity in a transgenic Caenorhabditis elegans model. The protective effects of Quanxie (Scorpio) on stroke have been investigated as a component herb in prescription. A prescription including Quanxie (Scorpio) decreased brain water content as well as neuronal injury via promoting proliferation of glialocyte and absorption of hematoma in a cerebral hemorrhage rat model. Another prescription decreased cerebral edema and capillary permeability in an acute brain hypoxia rat model.

**Wugong (Scolopendra)**

Wugong (Scolopendra) is a dried body of Scolopendra subspinipes mutilans L. Koch. The clinical usage is similar to Quanxie (Scorpio). To date, Wugong (Scolopendra) extracts, compounds and other peptides showed anti-oxidant effects, analgesic effects on neuropathic pain via deactivations of microglia and astroglia, AChE inhibitory activity, inhibitory effects on neuroinflammation in an amyotrophic lateral sclerosis animal model using hSOD1G93A transgenic mice, and neuroprotective effects on a PD model as a mixture with L-dopa. In the field of stroke, ethanol extract of Wugong (Scolopendra) ameliorates brain damage via inhibiting the thrombotic process or anti-thrombogenesis, and via up-regulation of neuroglubin in the ischemic penumbra in MCAo rat model. Prescription containing Wugong (Scolopendra) enhanced the differentiation and proliferation of neural stem cells and protected against brain damage in the MCAo rat model.

**Dilong (Pheretima Aspergillum)**

Dilong (Pheretima Aspergillum) is a dried body of devined Pheretima aspergillum Perrier or allied species. It has been used clinically for the treatment of loss of consciousness induced by high fever, fright epilepsy and convulsions, painful impediment of joint, numbness, hemiplegia, cough and dyspnea induced by lung heat, edema, and dysuria. The neuro-pharmacological activities of Dilong (Pheretima Aspergillum) extracts, compounds, peptides or its prescriptions have been well-documented. A peptide of Dilong (Pheretima Aspergillum), lumbricisin reduced 6-hydroxydopamin-induced-neuronal apoptosis in vitro and in vivo. It ameliorated the motor impairments in disease PD mouse model. In addition, Dilong (Pheretima Aspergillum) compounds increased the learning and memory abilities and decreased the abnormal behaviors of the AD mouse model and increased the activities of SOD and Glutathione peroxidase and decreased the amount of malondialdehyde in the brain tissues. In the field of stroke, enzymatic extract of Dilong (Pheretima Aspergillum) reduced cerebral infarction and improved neurologic deficits water extract of Dilong (Pheretima Aspergillum) reduced brain damage and functional deficits via inhibiting glial proliferation and S100B proteins, inhibiting oxidative toxicity and inflammatory cytokines, and inhibiting neuronal apoptosis and edema in the MCAo rat model. The activities of the prescriptions containing Dilong (Pheretima Aspergillum) along with Buyanghuanwu decoction (BHD) on ischemic stroke and vascular dementia have also been reported. BHD is most commonly prescribed for stroke rehabilitation and its neuropharmacological activities are well documented including protective effect on hypoxia induced neuronal damage, neuroprotective effects, neurogenic effect, functional recovery effect in vascular dementia, and angiogenetic effect in focal cerebral ischemia.
**DISCUSSION**

In the current study, we reviewed the literature for studies related to the liver-pacifying medicinal. Some of the characteristics of the medicinal are summarized below.

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. The pharmacological effects of liver-pacifying medicinal on CNS diseases, including PD, AD, stroke and epilepsy are likely their most important effects and hence, have been extensively studied. Traditionally, liver-pacifying medicinal have been considered the major medicines for relieving brain-related symptoms, including tremor, convulsion, headache, and vertigo. Pharmacokinetic studies on the major components of RG, RURU, and SCO are also supportive. After intravenous injection, gastodrin, a major component of RG, is rapidly distributed to the brain, with peak concentration at 15 min, and half-life of 60 min. The metabolite HBA is also detected in the brain 165 min after injection. Its compounds including phospholipids or sphingolipids showed neuroprotective effects by stimulation of nerve growth factor (NGF) synthesis in astrocytes and enhanced the action of NGF in terms of neurite outgrowth from PC12 cells. Prescriptions including BB showed anti-epileptic effects on penicillin-induced chronic epilepsy model via GABA enhancement and glutamate inhibition, and neuroprotective effects on cerebral ischemia model via reducing aquaporin 4 and MMP-9 mRNA expression.

BB

BB is the dried hardened larvae of Bombyx mori L., infected by Beauveria bassiana (Bals.) Vuillant. It has been used clinically for the treatment of fright epilepsy and convulsions, infantile convulsion, tetanus, deviated eye and mouth, wind-heat headache, hyperemia, throat pain, rubella, pruritus, supplicative parotitis, and mumps. The major pharmacological activities of BB include anti-coagulant effects, neuroprotection, neurotrophic effects, and anti-epileptic effects. Briefly, BB water extract prevented Aβ-induced cytotoxicity and maintained SOD activity in cultured rat astrocytes; additionally, it protected hippocampal neurons against excitatory amino acid-induced neurotoxicity. Its compounds including phospholipids or sphingolipids showed neuroprotective effects by stimulation of nerve growth factor (NGF) synthesis in astrocytes and enhanced the action of NGF in terms of neurite outgrowth from PC12 cells. Prescriptions including BB showed anti-epileptic effects on penicillin-induced chronic epilepsy model via GABA enhancement and glutamate inhibition, and neuroprotective effects on cerebral ischemia model via reducing aquaporin 4 and MMP-9 mRNA expression. Therefore, BB might pass through the blood-brain barrier and act directly on neurons or on the neural network to provide protective effects against brain disease. The pharmacological effects of liver-pacifying medicinal on CNS diseases, including PD, AD, stroke and epilepsy are likely their most important effects and hence, have been extensively studied. Traditionally, liver-pacifying medicinal have been considered the major medicines for relieving brain-related symptoms, including tremor, convulsion, headache, and vertigo. Pharmacokinetic studies on the major components of RG, RURU, and SCO are also supportive. After intravenous injection, gastodrin, a major component of RG, is rapidly distributed to the brain, with peak concentration at 15 min, and half-life of 60 min. The metabolite HBA is also detected in the brain 165 min after injection. Its compounds including phospholipids or sphingolipids showed neuroprotective effects by stimulation of nerve growth factor (NGF) synthesis in astrocytes and enhanced the action of NGF in terms of neurite outgrowth from PC12 cells. Prescriptions including BB showed anti-epileptic effects on penicillin-induced chronic epilepsy model via GABA enhancement and glutamate inhibition, and neuroprotective effects on cerebral ischemia model via reducing aquaporin 4 and MMP-9 mRNA expression.
drugs for rehabilitation. Results of clinical use of liver-pacifying medicinal for stroke suggest that they may be appropriate during the phase in which abnormal symptoms of the skeletonmuscular system occur i.e., paralysis, numbness, and tremor.  

Yun et al. 176 reported that the therapeutics for stroke are mostly described in the chapter on wind syndrome of "Dongeuibogam", in which, 92 prescriptions were described. However, they did not analyze the prescription by the pathological phase of stroke. Our analysis suggested that 3 in 19 prescriptions that are described with the term “Zu” or “Ji” contain liver pacifying medicinal, whereas, 32 in 73 prescriptions that do not describe those terms, contain liver pacifying medicinal. This is also supported by reports showing that extracts and components of RG, RURU, SCO, Quanxie (Scorpio), Wugong (Scolopendra), BB, and Dilong (Pheretima Aspergillum) improve neurological function in the convalescent phase by modulating factors related to function, including neurotrophic factors.  

RURU also exhibits angiogenic activities via increases in VEGF and basic fibroblast growth factor, 46 which is considered as one of the recovery processes in ischemic brain tissue. 

On the basis of literature review and clinical use in traditional medicine, liver-pacifying medicinal might be useful in the treatment of stroke via direct or indirect action on neurons during the disease process, especially from the subsacute phase up to the convalescent phase. Additional studies might be needed to investigate the effects of combination therapy with other neuroprotective agents, rehabilitation therapeutics and other traditional medicines of various activities, in order to determine more effective treatments for stroke in traditional medicine.

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