Phytomedicine 9: 478–484, 2002

http://www.urbanfischer.de/journals/phytomed

Phytomedicine

REVIEW

Stroke therapy in traditional Chinese medicine (TCM): prospects for drug discovery and development*

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Summary

Brain injuries resulting from stroke are a major and increasing public health problem in both developed and developing countries worldwide. China's extensive experience in the use of traditional Chinese medicines (TCMs) in stroke therapy indicates that TCM preparations are effective, with few or no side-effects. There are more than 100 traditional medicines in use for stroke therapy in China. Some of their therapeutic effects in stroke have been confirmed by recent clinical studies. A large number of compounds have been isolated from TCMs and most of these resources have not yet been characterized for pharmacological purposes. Here, this article explains how TCM provides an extensive and knowledge-rich foundation for implementing a strategically focused pharmacological research program aimed at the development of new drugs.

Key words: Chinese Medicine, stroke therapy, pharmacological research program

With an increasing population of elderly people, stroke is becoming a major health issue worldwide. The incidence of stroke has been reduced by preventive measures aimed at controlling hypertension, hypercholesterolaemia, substance abuse and smoking, and by the use of anti-coagulation drugs in specific high-risk groups (Fisher, 1995). Treatments that are aimed at dissolving clots and restoring blood flow, as well as therapies that block excitatory neurotransmission, prevent the ischaemic inflammatory response, or scavenge free radicals have all shown promising therapeutic potential in animal stroke models (Meldrum, 1995). Currently, a number of emerging stroke treatments are at the clinical trial stage (Koroshetz and Moskowitz, 1996). Treatment with tissue plasminogen activator (t-PA), a clot-dissolving drug, has been demonstrated to be an effective emergency treatment for acute ischaemic stroke, despite some risk from drug-induced intracerebral bleeding (Institute and Stroke Study Group, 1995). Other drugs that have been shown to be effective in animal experiments had to be withdrawn from clinical trials in humans because of serious adverse side-effects. Overall, no currently approved treatment consistently reduces stroke size or neurological disability in humans (Koroshetz and Moskowitz, 1996).

In China, stroke is treated using traditional Chinese medicine (TCM; Box 1), which has been developed over thousands of years. The therapeutic effects of Chinese medicines used for the treatment of stroke have been documented in a large body of almost exclusively Chinese literature (Zhou and Xiao, 1997). Nearly 50 journals (47 journals of traditional Chinese medicine and two journals of integrated traditional and Western medicine) ar publiched regularly in China that are devoted to TCM (Gastel and Weng, 1990). In a large

*Reprint from Current Trends Elsevier Science London TiPS **20**; 191–196 (1999)

0944-7113/02/09/05-478 $ 15.00/0

number of studies, the effectiveness of TCM stroke therapy has been evaluated based on the use of a scoring scheme developed for this purpose (Chen and Yang, 1991). Evaluation included the status of the patient's consciousness, language ability, mobility of upper and lower limbs and functional abilities before and after TCM treatment. Other factors contributing to the overall score included the treatment outcome, such as mortality or discharge to home, and the existence of other medical complications. Clinical data from those studies suggest that TCM stroke medicines are effective and merit further investigation. The abundant clinical data and extensive experience with TCMs in humans can serve as a strong basis for intensified basic pharmacological research aimed at elucidation of the active components and mode of (synergistic) action of TCMs.

In recent years, a great deal of pharmacological research has been undertaken to review and establish reliable composite formulae of TCM natural products (Wang et al., 1995). A number of commercial stroke treatments based on TCM such as "Hu Xin Dan", "Puerarin injection", "Shen Mai injection" and others have been introduced into the market recently, after extensive pharmacological research and clinical trials (Tianjin, 1996; Chiatai, 1993). Attempts have also been made to document research data from extracts of TCM natural products according to orthodox pharmacological actions (Chen, 1995). Many different TCM ingredients are screened for effectiveness in a specified biological assay or test system. A number of active compounds have been isolated and shown to have pharmacological activity in animal models (Chen et al., 1998; Li et al., 1997; Wang et al., 1997; Yu et al., 1997; Zhong et al., 1997). However, the use of TCM formulae containing multiple components complicates pharmacological research aimed at the isolation of active compounds. The therapeutic efficacy of a mixture and the lack of efficacy of isolated compounds may be due to pharmacokinetic or pharmacodynamic synergism of the ingredients. Therefore, in a complimentary approach, the effects of complex TCM preparations are investigated in a comprehensive battery of tests.

Pharmacology of TCM stroke therapeuticals

In TCM, drugs for stroke therapy have been classified broadly into four groups according to their primary mode of action. More than 100 Chinese medicines have been used for stroke prevention and therapy (Zhou and Xiao, 1997). The most commonly used TCM drugs for stroke therapy and some of their active components are listed in Table 1 (Huang, 1994). The chemical structures of some previously identified active components are shown in Fig. 1. The drugs in the first category are generally used in so called "channel-collateral stroke" patients. These drugs are most closely linked to essential TCM philosoophical principles (Box 1) and are thus the least accessible to "modern" pharmacological research.

Anti-inflammatory drugs

The second group of drugs can be classified as anti-inflammatory drugs. It should be noted in this context that the non-steroidal anti-inflammatory drug aspirin, which itself was originally isolated from the willow bark, was recently shown to protect rat neurons in primary culture and in hippocampal slices from glutamate-induced neurotoxicity (Grilli et al., 1996; Picano and Annracchio, 1998). More importantly, the aspirin effect was a result of the specific inhibition of the transcription factor NF-κB and not the result of inhibition of cyclooxygenase (Barner, 1995). It is conceivable that TCM anti-rheumatic drugs might contain novel substances with aspirin-like inhibitory activity on NF-κB or on other, yet uncharacterized, transcription factors involved in excitotoxicity.

Anti-thrombotic drugs

It has long been recognized in TCM that the main function of drugs in the third category is to clear obstructed blood vessels and to promote blood circulation. Based on the accumulated TCM evidence and the data from pharmacological studies, it can be expected that drugs in this group may be a potential source for the isolation of antithrombotic and/or thrombolytic compounds.

A number of TCMs have been shown to inhibit thrombogenesis and dissolve thrombosis. Single drugs, such as Rhizoma Ligustici and Radix Salviae miltiorrhizae, etc. have been reported to show good clinical effect in improving blood circulation and regulatiing "Qi" flor (Huang, 1994; Chen and Chen, 1992). Tetramethylpyrazine and cnidiumlactone, two biologically active compounds extracted from Rhizoma Ligustici were shown to relieve arteriolar spasm, accelerate blood flow and increse blood volume, and thus improve the disordered microcirculation (Chen and Chen, 1992). Tetramethylpyrazine reduced the plasma levels of β-TG (β-thromboglobulin), PF_4 (platelet factor 4) and TXB_2 (thromboxane B) (Huang, 1994). Similar therapeutic acctions in terms of increasing cerebral blood flow and inhibiting blood platelet aggregation and thrombolysis were found with Radix Salviae Miltiorrhizae, Radix Angelicae Sinensis, Radix Ginseng, *Radix Stephaniae tetrandrae* and *Radix Paeoniae rubrae* both *in vitro* and *in vivo* (Huang, 1994; Chen and Song, 1992; Liu and Xiao, 1992; Wang et al., 1996; Wu et al., 1990). Active

Box 1. A primer in traditional Chinese medicine stroke therapy.

Traditional Chinese medicine (TCM) has been used in China for thousands of years. The theoretical system of TCM is based on the doctrines of "Yin-Yang", the "Five Elements", "Zang" and "Fu" organs (viscera), and "Meridians" (Channels and Collaterals (Xu, 1991). TCM differs from Western medicine not only in specific diagnostic techniques and therapeutic principles, but also in its interpretation of both normal physiological function and pathological changes in the human body. In particular, TCM ppostulates a unique, inextricable relationship between the human body and its environment. Body and environment have to be in a relative balanced state to maintain the body's normal physiological function. When this balance is compromised, however, disease results.

Yin-Yang theory of TCM

In TCM, the Yin-Yang theory is important for diagnosis and treatment. Yin is the philosophical partner of Yang. They refer to two fundamental principles that oppose and complement each other. TCM analyses the relationship between the pathogenic factors and the patient using a dynamic viewpoint so that the inner character of the disease can be discerned. This type of organ dysfunction cannot be observed by routine examinations and symptoms cannot be curred by Western medicine. However, TCM can cure such patients with a tonic that is specifically added in the TCM prescription to nourish Yin.

Fundamental and incidental aspects of disease

In TCM, the occurrence and symptoms of diseases are determined by so-called fundamental and incidental aspects. The fundamental aspects concern body resistance, the cause of disease, primary onset of disease and disease with roots inside the patient. The incidental aspects, by contrast, comprise the pathogenic factors, the particular manifestations of the disease, complications of the disease and disease in the exterior context (outside) of the patient. As a general principle, TCM emphasizes the treatment of the fundamental aspects of disease.

Diagnostic principles

The classic diagnostic methods such as inspection, auscultation, olfaction, palpation and interrogation have also been developed over thousands of years in TCM. Among these examination techniques, pulse taking is a diagnostic method that is unique to TCM. A TCM doctor can detect conditions of illness and gather clinical data by carefully examining a patient's pulse. More than 20 different types of pulse characteristics have been described in TCM. The characteristics of the patient's tongue provide other important diagnostic dues in TCM. According to TCM theory, the face and the tongue have a close relationship to the five Zang and the six Fu organs. Because problems of the Zang and Fu organs can be most easily diagnosed by inspection of the face and tongue, their general appearance and colour are commonly examined first.

Therapeutic principles

TCM therapy is based foremost on an accurate diagnosis. After a thorough evaluation comprising the patient's history and the description of the signs and symptoms of the disease, determination of its cause is based on an analysis of the syndrome presented by the patient in the context of basic TCM nosology. TCM emphasizes the importance of recognizing dynamic changes in presenting symptoms during the course of disease. Different treatments will be applied at different stages in the course of the disease.

TCM prescriptions generally consist of a mixture of ingredients. The rationale for the use of complex TCM formulas rather than individual drugs is threefold. First, complex formulae are thought to maximize the therapeutic efficacy by enhancing the effects of individual ingredients, which may act synergistically. Second, complex formulae are designed such that different ingredients cover the variation of symptoms to be treated. Third, complex formulae are believed to ameliorate or prevent adverse side-effects linked to the toxicity of individual drugs and thus have better overall therapeutic efficacy.

Wind stroke

The diagnostic criteria for stroke are comparable in TCM and Western medicine. The TCM view of stroke differs from the modern scientific view with respect to the aetiology and pathogenesis of the cerebral insult. The TCM equivalent of stroke is a syndrome called "wind stroke", which is characterized by facial paralysis, dysphasia, or aphasia and/or hemiplegia. According to TCM theory, wind stroke is generally the consequence of an inherent defect caused by "inter-

compounds isolated from herbs include tanshinone (Radix Salviae Miltiorrhizae), angelo and glabralactone (Radix Angelicae Sinensis), ginsenosides from ginseng, tetrandrine (Radix Stephaniae Tetrandrae) and paeoniflorin (Radix Paeoniae Rubra). Paeoniflorin, angelo and glabralactone have been shown to possess greater potency and longer-lasting therapeutic action in terms of increasing cerebral blood flow than papaverin (Huang, 1994). "Bu Yang Huan Wu decoction", which contains Radix Angelicae Sinensis, Radix Paeoniae Rubra, Lumbricus, Flos Carthami and others inhibited thrombosis by stimulating the vessel wall to release factor VIII and inhibited the activity of coagulating fibrinogen (Bian and Zhou, 1995).

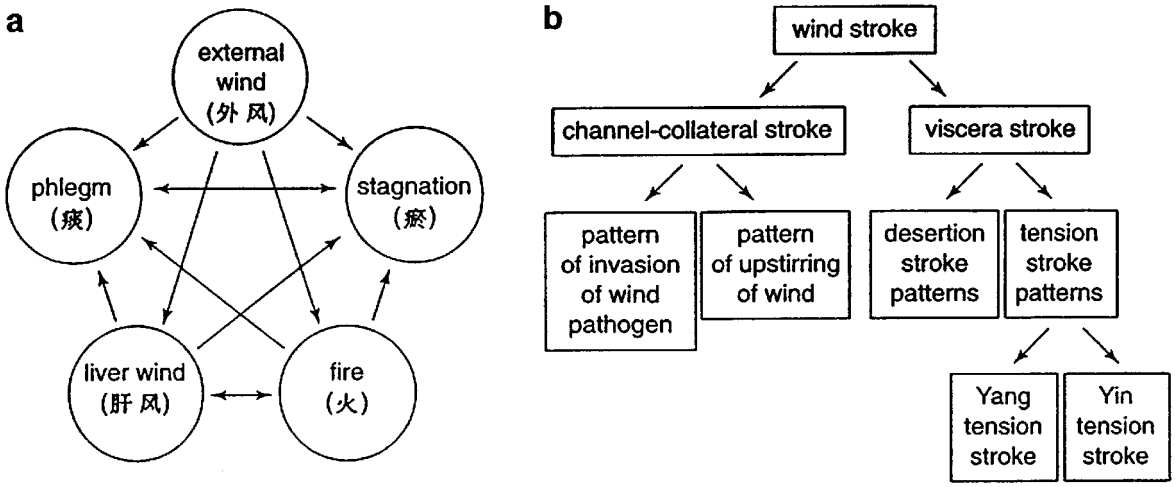

Fig. 1. a: Relationships and interactions of the five pathogenic factors causing "wind stroke" and **b:** patterns of wind stroke based on traditional Chinese medicine (TCM). The aetiology of wind stroke may involve "external wind", "internal liver wind", "phlegm", "fire" and "stagnation" according to TCM. These factors can interact with each other. Based on the pathognomonic symptoms associated with it, wind stroke, including the related syndromes designated "viscera stroke" (with loss of consciousness) and "channel-collateral stroke" (without loss of consciousness) can be considered to correspond to cerebrovascular disease including cerebral interaction due to cerebral haemorrhage or ischaemia, and subarachnoid haemorrhage. In particular, the condition designated viscera stroke is the TCM counterpart of cerebral haemorrhage-induced stroke whereas the syndrome named channel-collateral stroke is similar to cerebral transient ischaemic attacks. Depending on the presence of various additional clinical symptoms, both channel-cullateral stroke and viscera stroke can be divided into different subcategories.

nal wind" and "external pathogenic wind". Under certain circumstances, external pathogenic wind, internal wind, "phlegm", "fire", "stagnation" and their interactions may lead to Yin or Qi weakness, "liver fire", "wind-phlegm", "phlegm-dampness", or "blood stasis". The result would be an imbalance between Yin and Yang, disturbance of the blood and Qi circulation, deficiency of "liver-Yin" and "kidney-Yin", stagnation of phlegm and dampness. All these can lead to the sudden onset of wind stroke. The relationships of the five pathogenic factors causing wind stroke and patterns of wind stroke according to TCM are shown in Fig. 1.

The treatment of wind stroke in TCM is aimed at alleviating the patient's symptoms and at eliminating the underlying cause. The basic approach in the treatment of wind stroke takes into account the equilibrium of the relative strengh between the patient's body resistance and the intensity of endogenous and exogenous pathogenic factors. The restoration of the patient's resistance and the elimination or weakening of the intensity of pathogenic factors are important. In an effort to modulate the general physical resistance of stroke patients, a number of approaches are available that are unique to TCM. Furthermore, TCM emphasizes the importance of recognizing dynamic changes of symptoms during the course of the disease. Different prescriptions will be used at different stages of the disease, and further adjusted to suit the individual patient's condition (Wu and Fischer, 1997).

Neuroprotective drugs

Drugs listed in the fourth category in Table 1 are used to treat neurological symptoms and sequelae of stroke such as spasm or opisthotonus accompanied by high fever, dizziness, strong headaches, flushed face, sudden syncope and facial paralysis. At present, this group of drugs is the least studied in pharmacological TCM research. Evidence for "neuroprotective" properties of TCMs has been inferred primarily by indirect means and is limited to a rather small number of TCM ingredients. However, some of the drugs might represent a potential source for the isolation of neuroprotective compounds. For example, it was reported that ginsenosides significantly increased the survival of mice under acute

Table 1. Traditional Chinese medicines used in stroke therapy and known active components (Huang, 1994).

Medicine	Scientific name	Chinese	Main components
Drugs for treatment of exterior syndrome (diaphoretics), clearing away internal heat (antipyretics)			
Radix Ledebouriellae	*Ledebouriella divaricata*	防风	Octanal, β-bisabolene, nonanal, β-eudesmol
Rhizoma Notopterygii	*Notopterygium incisium*	羌活	Bergamonttin, isoimperation
Herba Asari	*Asarum heterotropoides*	细辛	Methyleugenol, safrole
Radix Rehmanniae	*Rehmannia glutinosa*	地黄	Campesterol, catalpol and rehmannin
Radix Paeoniae Rubra	*Paeonia lactiflora*	赤芍	Paeoniflorin, paeonine
Radix Scutellariae	*Scutellaria baicalensis*	黄芩	Baicalin, wogonoside, wogonin and baicalein
Herba Menthae	*Mentha haplocalyx*	薄荷	Menthol and menthone
Flos Chrysanthemi	*Chrysanthemum morifolium*	菊花	Chrysanthemin
Radix Bupleuri	*Bupleurum chinense*	柴胡	Saikoside, saikogenin, adonitol and stimasterol
Periostracum Cicadae	*Cryptotympana pustulata*	蝉蜕	Amino acids
Poria	*Poria cocos*	茯苓	β-Pachyman
Drugs for relieving rheumatism (antirheumatics)			
Radix Angelicae Pubescentis	*Angelica pubescens*	独活	Angelo, osthol, bergapten, glabralactone
Radix Gentianae Macrophyllae	*Gentiana macrophylla*	秦艽	Gentianine, gentianidine, gentianol
Radix Stephaniae tetrandrae	*Stephania tetrandra*	防己	Tetrandrine, berbamine and cyclanoline
Ramulus Mori	*Morus alba*	桑枝	Alkaloids
Ramulus Loranthi	*Loranthus parasiticus*	桑寄生	Avicularin and quercetin
Drugs for promoting the circulation of blood and removing stasis			
Rhizoma Ligustici	*Ligusticum chuanxiong*	川芎	Cnidiumlactone, cnidilide, tetramethylpyrazine
Radix Salviae Miltiorrhizae	*Salvia miltiorrhiza*	丹参	Tanshinones I, II, IIA, IIB; isotanshinones I, II
Semen Persicae	*Prunus persica*	桃仁	Amygdalin, amygdalinase and allantoinase
Flos Carthami	*Carthamus tinctorius*	红花	Carthamin, carthamone
Herba Leonuri	*Leonurus heterophyllus*	益母草	Leonurine, stachydrine and leonuridine
Radix Achyranthis bidentatae	*Achyranthes bidentata*	牛膝	Ecdysterone and inoteosterone
Drugs for calming the liver and subduing wind			
Cornu Saigae tataricae	*Saiga tatarica*	羚羊角	Proteins and lipids
Concha Haliotidis	*Haliotis diversicolor*	石决明	Proteins and lipids
Rhizoma Gastrodiae	*Gastrodia elata*	天麻	Gastrodin
Ramulus Uncariae cum Uncis	*Uncaria rhynchophylla*	钩藤	Isorhynchophylline, corynoxeine
Bombyx Batryticatus	*Bombyx mori*	僵蚕	Ecdysterone and 3-hydroxykynurenine
Scorpio	*Buthus martensi*	全蝎	Katsutoxin, neurotoxin I, II
Scolopendra	*Scolopendra subspinipes*	蜈蚣	Chitosan, glucosamine, d-hydroxylysine
Lumbricus	*Pheretima asiatica*	地龙	Hypoxanthine, lumbrifebrin, lumbritin

hypoxia and protected the brain from ischaemic and reperfusion injuries (Zhang and Liu, 1996). The protective effects of ginsenosides in decreasing intracellular Ca^{2+} has been attributed to increased ATPase activity (Jiang et al., 1996). In addition, the ginsenosides significantly inhibited free-radical generation by xanthine-xanthine oxidase (Li et al., 1997). "Nao Yi An", a complex formula that is used in the treatment of intracerebral haemorrhage, has been suggested to possess neuroprotective properties by inhibiting NADPH-diaphorase, an enzyme involved in the production of nitric oxide (NO), which has been implicated in excitotoxicity (Peng et al., 1997). Rhizoma Gastrodiae (gastrodin) and Ramulus Uncariae (corynoxeine) decoction significantly inhibited the formation of lipid peroxides in the brain of rats (Du et al., 1991). Similar neuroprotective effects were also observed after treatment with Rhizoma Gastrodiae, Radix Salviae Miltiorrhizae and tetramethylpyrazine (Huang, 1994; Gao et al., 1995; Xiao and Ge, 1993). Finally, recent studies showed that tetrandrine and its derivative daurisoline had significant protective effects against ischaemic injury with greater protection from NO-dependent neurotoxicity (Che e tal., 1996; Wang et al., 1998). The neuroprotective effect of daurisoline was mediated by blocking Ca^{2+} influx into cells (Liu et al., 1998).

It will be interesting to see whether these or similar drugs belonging to the same TCM category potentially contain glutamate receptor antagonists, substances that interfere with the formation of neurotoxic free radicals, or compounds with other, yet uncharacterized, neuroprotective effects.

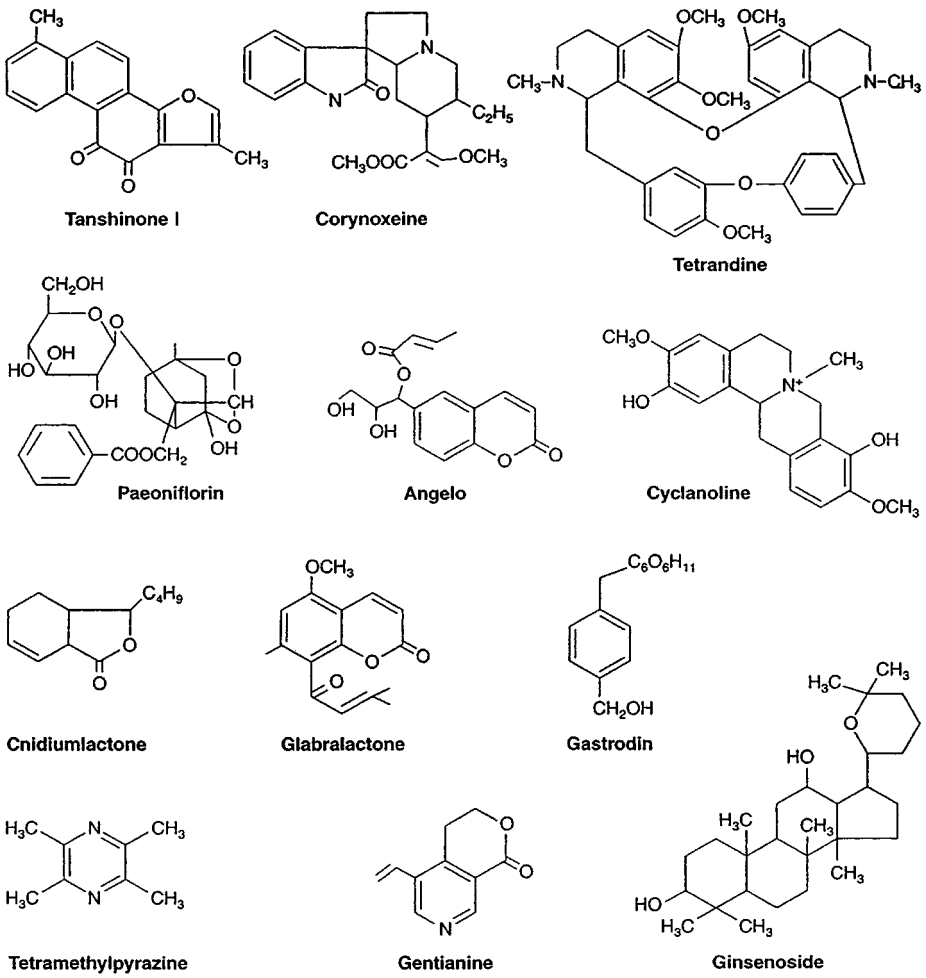

Fig. 1. Chemical structures of some active components from traditional Chinese medicines used for "wind stroke" therapy. Tanshinone from Radix Salviae miltiorrhizae showed anti-thrombotic activity (Wang et al., 1996). Tetramethylpyrazine and cnidiumiactone extracted from Rhizoma Ligustici were reported to improve blood circulation in patients (Chen and Chen, 1992). Paeoniflorin from Radix Paeoniae rubrae and angelo and glabralactone from Radix Angelicae pubescentis have been shown to increase cerebral blood flow in humans (Huang, 1994). Gentianine from Gentianae Macrophyliae and cyclanoline from Radix Stephaniae tetrandrae improved the microcirculation in stroke patients (Huang, 1994; Xie et al., 1994). Gastrodin from Rhizoma Gastrodiae and corynoxeine from Ramulus Uncariae cum Uncis sigificantly inhibited the formation of lipid peroxides in the brain of rats (Du et al., 1991). Ginsenosides from ginseng protected brain from ischaemic and reperfusion injuries in rodents (Liu and Xiao, 1992; Zhang and Liu, 1996). Similar neuroprotective effects were also observed after treatment with gastrodin, tanshinone, tetramethylpyrazine and tetrandrine (Huang, 1994; Gao et al., 1995; Xiao and Ge, 1993). Neuronal function was assayed by electrophysiological recording (tanshinone), learning and memory tests (gastrodin) and ischaemic animal models (tetramethylpyrazine and tetrandrine) (Huang, 1994; Gao et al., 1995; Xiao and Ge, 1993).

Concluding remarks

China's long experience in the use of traditional Chinese medicines indicates that they are effective in stroke therapy and have few or no side-effects (Xu, 1991). Groups of TCM drugs have been identified as potential sources for compounds with predominant effects on the circulation, thrombogenesis, inflammatory processes and neuroprotection. Both basic and clinical research in TCM will benefit from increasing international collaborations with Chinese scientists and physicians. The integration of Chinese TCM and Western pharmacology constitutes a potentially rich source for drug discovery and development.

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