Editorial

Herbal Medicine in Stroke
Does It Have a Future?

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The lack of effective and widely applicable pharmacological treatments for ischemic stroke patients may explain a growing interest in traditional medicines, for which extensive observational and anecdotal experience has accumulated over the past thousand years. The World Health Organization (WHO) defines traditional medicine as “health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being.” Unlike Western medicine, which focuses on disease, traditional medicine takes the approach that the body provides external clues to an internal imbalance that can be addressed by interventions such as herbs and acupuncture (holistic treatment approach). According to a 2003 WHO report, traditional medicine is very popular in all developing countries, and its use is rapidly increasing in industrialized countries. For example, traditional herbal preparations account for 30% to 50% of the total medicinal consumption in China. In Europe, North America and other industrialized regions, over 50% of the population have used traditional medicine at least once. The global market for herbal medicines currently stands at over US $60 billion annually and is growing steadily.

In recent years, several reviews have been published on the effect and potential benefits of traditional Eastern medicine in stroke. It has been suggested that some herbal medicines, or their products, may improve microcirculation in the brain and protect against ischemic reperfusion injury, possess neuroprotective properties and inhibit apoptosis, thus justifying their use in ischemic stroke patients. However, unlike industrially manufactured pharmacological drugs used in Western medicine, the active (potent) components of herbal medicines often have not been specified and measured precisely, although there have been recent attempts to regulate dosages and use of these medicines by some governments. This inevitably leads to variations between formulations and batches of the same herbal medicines and, as a consequence, to difficulties in the evaluation and comparison of the results of trials testing these medicines. The issue is further complicated by the fact that most publications on the efficacy of herbal medicines are published locally in non-English languages, thus making their retrieval and appraisal very difficult for specialists outside that region. Therefore, any efforts to systematically analyze and present the existing clinical evidence on the efficacy of herbal medicines to English-speaking audiences should be welcome.

In this issue of Stroke, Wu and colleagues present the first systematic review of the efficacy and safety of 59 Traditional Chinese Patent Medicine* (TCPM) drugs listed in the Chinese National Essential Drug list (2004) and commonly used in China for ischemic stroke patients. The authors tried to apply Cochrane systematic review methodology to their review, and chose death/dependency and adverse events at 3 months of follow-up as the primary outcome measures. Six reviewers independently selected the studies and extracted the data, which reduced the potential for bias and errors. Their thorough literature search (1966–2005) of both published and unpublished Chinese and non-Chinese language literature yielded 5 definitely randomized, 115 possibly randomized and 71 nonrandomized controlled clinical trials (19 338 patients in total) conducted in China to evaluate the efficacy of 22 TCPM drugs (no eligible trials were identified for the remaining 37 TCPM drugs). The authors correctly stress the poor methodological quality of almost all (97%) the clinical trials selected for the review. The pooled analysis of trials (randomized and nonrandomized combined) showed a strikingly large and significant (odds ratio [OR] 3.4, 95% CI 3.1 to 3.6) positive effect of almost all TCPM treatments (21 of 22) analyzed in improving neurological impairment (over 3-fold improvement compared with controls) and an extremely low (3%) case-fatality in 10 trials that reported death outcome, again, in favor of the treatment group (OR 0.5, 95% CI 0.2 to 0.9). However, only 2 trials (both with adequate concealment of randomization) reported primary outcomes (death or dependency), and no difference was found in these trials between treatment and control groups. The extremely low case-fatality is most likely to be explained by a highly selected group of patients included in these trials, although reporting bias (underreporting) cannot be excluded. No statistically significant difference in adverse events between treatment and control groups on 14 TCPM analyzed was found in 38 trials that reported adverse events, although it remains unclear whether adverse events were registered but not reported in the remaining 57 trials included in the analysis of adverse events.

*Chinese patent medicines refer to finished or formulated products (eg, capsules) made from crude herbs.
The authors have reached 4 major conclusions, only 2 of which seem reasonably supported by the evidence they provided. First, based on the overall poor methodological quality of trials included in the review they conclude that there is insufficient evidence on the effects of TCPM in ischemic stroke. This conclusion seems reasonable and is in line with results of 2 recent Cochrane systematic reviews that analyzed 2 TCPM drugs (Ginkgo biloba and Dan Shen agents),6,7 which are listed among 59 TCPM included in the current review. However, it would have been methodologically better if the authors had not analyzed all clinical trials irrespective of their methodological quality but instead analyzed trials of acceptable methodological quality alone or at least separately. The authors also did not provide references to trials and TCPM drugs listed in their Table 1 and Figures 1 and 2, thus making the interpretation of the results difficult. It is unclear why they did not include in the analysis some TCPM drugs currently analyzed by the Cochrane Collaboration for the treatment of acute ischemic stroke.12–14 Second, based on the existence of 2 randomized controlled trials of acceptable methodological quality the authors argue that TCPM can be evaluated in a randomized controlled trial setting. This conclusion also seems reasonable, although the authors did not provide clear guidelines for the desirable design of future trials that would address some important issues specifically pertaining to the proper evaluation of herbal medicines in ischemic stroke patients, such as complexity of the components of herbal medicines, or dosage and timing of the intervention. Third, the authors conclude that data concerning adverse events associated with TCPM drugs were reassuring. Given the very high likelihood of multiple biases in the trials analyzed (eg, selection, measurement, and reporting biases) and the fact that adverse events for 6 TCPM drugs analyzed (2 of which were tested in randomized controlled trials of acceptable methodological quality) were significantly higher than in controls, this conclusion seems overstated. The absence of analysis for publication bias and the authors’ inability to obtain missing data from relevant trialists make this and other conclusions of the review less certain. Fourth, the authors recommend 8 TCPM drugs (Milk vetch, Mailuoning, Ginkgo biloba, Ligustrazine, Danshen agents, Xuesetong, Puerarin, and Acanthopanax) for further research, justifying their selection by the number of studies and patients in which these drugs have been studied compared with other drugs. This justification is not convincing. The choice of TCPM drugs for further clinical testing should be largely based on their efficacy and safety profiles established in preclinical and early clinical (phase I and IIa trials) research, evidence which is not yet available for most of these herbal medicines.

So, what lessons can we learn from this systematic review? There are at least 2 important and inter-related lessons. First of all, it is clear that there is great interest among Chinese researchers in studying efficacy of TCPM drugs in ischemic stroke patients. Therefore it is important to develop statutory regulations and approval process that would allow the development of scientifically sound and locally applicable guidelines to study these medicines appropriately. Given the widespread use of traditional medicines across the world, it is important to regulate and establish educational and practice standards for practitioners practicing these medicines.15 Efforts should be made to extract and study active components from allegedly efficient herbs that may be a basis for new pharmacological agents for ischemic stroke patients.16 Secondly, existing evidence is insufficient to either refute or support the use of TCPM as a treatment in acute and subacute ischemic stroke patients. It should be noted that these drugs are not side-effect free (including direct toxic reactions to the herbs, interactions with other medicines, allergic reactions, and idiosyncratic reactions) and caution should be exercised in their use, especially outside of clinical research and clinically monitored settings. Only properly designed clinical research will be able to reliably address questions regarding the efficacy, efficiency and safety of these drugs in ischemic stroke patients. The widespread and increasing use of herbal medicines throughout the world cannot be ignored any longer by Western medicine. This is reflected in some newly available funds for studying traditional medicine (eg, funds and research projects of the National Center for Complementary and Alternative Medicine of the National Institutes of Health). This, together with the ever increasing burden of stroke in the world, especially in low- and middle-income countries,17 justifies the urgent need to evaluate herbal medicines in properly designed randomized controlled trials, followed by appropriate meta-analysis. However, there are several issues specifically pertaining to clinical testing of herbal medicines in stroke patients that need to be addressed in the design of such trials. These include, for example, the difficulty of using placebo-controlled design in countries where herbal-based treatments are regarded as a standard, such as China; difficulty of developing a placebo intervention that would not be different from active herbal intervention in terms of its taste, smell, and appearance; reluctance to report adverse events for fear of individual blame attributable to cultural beliefs in some Eastern countries or attributable to belief that some adverse effects (eg, diarrhea) are part of the normal response to herbal treatment; uncertainty and multi-component structure of active ingredients and other chemic compounds of herbal medicines that can be considered as complex interventions of varying dosages and interactions, especially in the context of differences in treatment concepts between Western and traditional medicines; timing, dosage and duration of the interventions. One possible approach to these issues may be to use study design options suggested by Campbell and colleagues for complex health-related interventions.18 Recently developed CONSORT guidelines19,20 should be used for reporting randomized, controlled trials of herbal interventions and which can form the basis for planning and conducting of such trials.20 Until scientifically sound evidence of the efficacy and safety of herbal medicine in ischemic stroke patients is available, efforts should be made throughout the world to continue implementing treatment strategies of proven effectiveness.

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References

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