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The challenge of traditional Chinese medicines for allopathic practitioners

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THE STUDY REPORTED BY Zhang et al. (14) in this issue of the *American Journal of Physiology-Heart and Circulatory Physiology* raises several potentially important issues relating to traditional remedies. Despite their lack of acceptance by opinion makers in the field of clinical medicine, these remedies remain the commonest therapeutic agents used worldwide, and some of them have even found their way into the pharmacopeias of several developed countries. Herbal remedies are approved in Germany and Japan (8). In the United States, it has been reported that ~25% of Americans who consult their physician about a serious health problem employ unconventional therapy, but only 70% of these patients inform their physician of such use (3). A recent survey revealed that general practitioners in Scotland currently prescribe herbal medicines more frequently than in the past decade. However, a distinction must be drawn between herbal (i.e., plant derived) remedies and medications used in traditional Chinese medicine. The latter often contains multiple animal products, and the ingredients are usually combined in accordance with principles very different from Western allopathic medicine.

Tongxinluo in capsule form is a compound formulated according to the meridian theory of traditional Chinese medicine. It is a mixture of plant and animal products (1) (Table 1) and was approved in 1996 by the State Food and Drug Administration of China for treatment of angina pectoris and ischemic stroke. The contents of the capsule have been shown to have a variety of effects that are potentially of therapeutic value, such as improving endothelial cell function, lowering lipids, reducing inflammation, preventing apoptosis, and enhancing angiogenesis (1).

Nevertheless, the report by Zhang et al. (14) describing the effect of Tongxinluo on plaque stability is interesting for several reasons. Briefly, the study was carried out to test the hypothesis that Tongxinluo, a Chinese traditional medicine, enhances stability of vulnerable plaques in a cholesterol-fed rabbit model of atherosclerosis. After 10 wk of feeding a diet supplemented with 1% cholesterol, five groups of animals were treated for 8 wk as follows: control group, three-dose levels of Tongxinluo, and high-dose simvastatin group. At the end of *week 16*, an adenovirus containing p53 was injected into the abdominal aortic plaques and plaque rupture was induced by pharmacological triggering 2 wk later. The incidence of plaque rupture in all treatment groups was significantly lower than that in the control group. The high-dose Tongxinluo and simvastatin groups had similar degrees of protection against plaque rupture.

Corrected acoustic intensity and fibrous cap thickness of the aortic plaques were significantly increased, whereas plaque area, plaque burden, vulnerable index, and expression of oxidized low-density lipoprotein receptor 1, matrix metalloproteinase 1 (MMP-1), MMP-3, tissue inhibitor of MMP 1, and nuclear factor-κB in plaques were markedly reduced in all treatment groups compared with the control group. Tongxinluo dose-dependently lowered serum lipid levels and inhibited systemic inflammation (high-sensitive C-reactive protein). Similar to the high-dose simvastatin group, the high-dose Tongxinluo group also exhibited a reduction in low-density lipoprotein cholesterol and oxidized low-density lipoprotein, a low-expression level of systemic and local inflammatory factors and a low-plaque vulnerability index. It was concluded that Tongxinluo dose-dependently enhanced the stability of vulnerable plaques and prevented plaques from rupture. Simvastatin and Tongxinluo offered similar protection in terms of lipid-lowering, anti-inflammation, and antioxidation effects. While the findings of the study are unequivocal, there are difficulties when one attempts to reconcile pathological studies performed in the allopathic tradition with therapies derived from an entirely different medical tradition.

Table 1. *Formulation of Tongxinluo capsule*

Ingredient	Components	%
Panax ginseng C. A. Mey. extract	Root and rhizome	1.7
Paeonia lactiflora Pall. extract	Root	1.6
Ziziphus jujuba Mill. Var. *spimosa* (Bunge) extract	Seed	1.2
Santalum album. extract	Heartwood of stem	0.4
Dalbergia odorifera extract	Heartwood of stem and root	4.0
Steleophaga plancyi (Boleny) Wingless cockroach (beetle)	Female dried body	18.1
Scolopendra subspinipes mutilans L. Koch red-headed centipede	Dried body	3.6
Hirudo nipponica Whitman leech	Dried body	27.3
Cryptotympana pustulata Fabricius cicada	Skin	18.1
Buthus martensii Karsch scorpion	Dried body	18.1
Boswellia carteri	Resin	6.0
Borneolum syntheticum	$C_{10}H_{18}O$	3.6

Although digoxin and aspirin, which have been in routine use for several decades, entered the medical world as herbal remedies initially, their use today is based on a rigorous control of manufacturing practices, which have permitted researchers to undertake placebo-controlled multicenter clinical trials. In contrast, the problems that bedevil traditional remedies are the lack of standardization, the paucity of controlled clinical trials, and their failure to address mechanisms of disease. Zhang et al. (14) have addressed the first of these problems by providing information regarding the constituents of Tongxinluo. The preparation is derived from a combination of plant and animal products, and the ingredients have been identified by HPLC. It appears that the variations in the concentrations of the various compounds in it are within clinically acceptable limits.

The authors elected to examine the potential role of Tongxinluo in stabilizing atherosclerotic plaques in a cholesterol-fed

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rabbit model and compared its effects with that of a positive control in the form of simvastatin. The findings clearly support the authors' claim that Tongxinluo reduces plaque rupture in their model. For the future, it would be of interest to determine whether all the compounds found in Tongxinluo have to be present in these precise proportions to produce the observed effects or whether they are due to the presence of a single ingredient. One would hope that the investigators would pursue these avenues not only to identify the active ingredient(s) but also to demonstrate their presence in blood, first in animal studies and later in human trials. Such experiments would permit them to inactivate the compound and perform an experiment with a negative control by way of confirmation of a therapeutic mechanism. Such an approach has been used in the examination of the effect of polyphenolic compounds present in grape seed extracts on endothelial function. In that instance, methylation of the OH groups in the molecule abolished the effect on endothelium-dependent relaxation (2).

This study also highlights certain exciting possibilities in the management of patients who are at risk of developing clinical manifestations of coronary heart disease. The conventional strategy for managing such patients is to stratify their global risk on the basis of cardiovascular risk factors. The Framingham risk score (4) is a convenient method of assessing the 10-year risk of developing a myocardial infarction or dying from one. In recent years, there has been a trend toward developing algorithms for identifying the short-term risk (e.g., 1- to 2-year risk). Much of this discussion centers on the idea of developing a method of diagnosing plaque instability from biomarkers in the blood or in the arterial wall. The former will likely be done from blood samples, and the latter could possibly be accomplished by radiological procedures that would permit an identification of components of plaques such as activated monocytes in the walls of arteries. The supporting data in the paper relating to the changes in blood and in the aorta provide a means of identifying markers of plaque instability in this particular model and may provide a basis of future clinical studies. Clearly, Tongxinluo has a potential role in this arena. Ironically, its use in the treatment of a specific disease (as defined in terms of the allopathic tradition) will in itself be a departure from certain principles of traditional Chinese medicine that would readily accept the proposition that two patients with the same disease could in fact be treated with different remedies.

A recent Cochrane Review of the use of this preparation in patients with unstable angina did not reveal evidence of an overwhelming benefit (3, 12), and the authors concluded that the 18 trials reviewed were at best of modest quality. However, in consideration of the findings of Zhang et al. (14), it could be suggested that patients with unstable angina were perhaps not the best group to demonstrate the therapeutic efficacy of Tongxinluo. It is recognized that one of the causes of unstable angina is plaque rupture (13). Thus it could be argued that such a diagnosis indicates that a potential therapeutic window for the compound has in fact closed. It would appear that long-term treatment of people with minimal coronary artery disease or those with chronic angina as opposed to unstable angina would be more likely to reveal evidence of clinical benefit (e.g., a reduction in major adverse cardiac events) through plaque stabilization. In this context it is important to remember that such patients would also be receiving conventional therapy for the management of their risk factors such as aspirin, β-blocker, statins, diuretics, nitrates, angiotensin-converting enzyme, and angiotensin receptor blockers. The presence of these conventional drugs in the body raises the possibility of significant drug interactions (see below).

As shown in Table 1, Tongxinluo is made up of 12 constituents, not all of which are derived from plants. Despite its efficacy in this animal model, it is likely that the preparation would require a significant degree of characterization in terms of both the active ingredients and profiles of their biological activity to satisfy the requirements of the regulatory bodies in the West such as the Food and Drug Administration (FDA) in the United States. For instance Hirudo powder is the desiccated body of *Thitmania pigra* Whitman, *Hirudo nipponica* Whitman, or *Whitmania acranulata* Whitman, which belong to the Hirudo family (5). It is likely to contain hirudin, which is a drug approved for human use as an anticoagulant. Another component of Tongxinluo, *Radix paeoniae rubra*, which is a derivative of the mulberry plant, has been the subject of an unfavorable review by the FDA because of a paucity of information. On that occasion, the FDA was unable to establish safety (10). Ginsenosides are known to interact with Coumadin and aspirin, and the Chinese Materia Medica notes that *Steleophaga plancyi* has antithrombotic effects. Studies with scorpion venom given intravenously to animals suggest that it may induce pressor responses by releasing norepinephrine from the sympathetic nerve terminals (6). Such considerations, when taken collectively, raise the possibility of side effects occurring with traditional remedies like Tongxinluo. Many Western proponents of traditional Chinese medicine have taken the view that these remedies have, a priori, only minimal side effects if used correctly. However, there are several instances of clinical problems created by these remedies through contaminants (11), disproportionate consumption of one of the constituents, and allergic reactions to proteins present in some animal products (7). Finally, some of these remedies are likely to influence the pathways involved in the cellular uptake of drugs (9). These are matters for concern that should be addressed and resolved at a future date by conducting large multicenter-controlled clinical trials. For the present, Tongxinluo in capsule form appears to be a stable formulation and shows promise as a plaque-stabilizing agent.

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