



Eastern Remedies for Western-type diet induced atherosclerosis

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Provenance and Peer Review: This article was commissioned by the Editorial Office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Comment on: Lu L, Qin Y, Chen C, et al. The atheroprotective roles of heart-protecting musk pills against atherosclerosis development in apolipoprotein E-deficient mice. *Ann Transl Med* 2019;7:714.

Submitted Feb 16, 2020. Accepted for publication Feb 29, 2020.

doi: 10.21037/atm.2020.03.39

View this article at: <http://dx.doi.org/10.21037/atm.2020.03.39>

In modern China, both Traditional Chinese Medicine (TCM) and evidence-based Western medicine are practiced side-by-side with an estimated 40% of all health care services based on TCM (1). TCM has a unique theoretical and practical approach to the treatment of disease and a longstanding history of practice of more than 3,000 years. It is based upon the central tenet of vital energy (*qi* or *ch'i*) that is circulating throughout the body to reach a status of health and wellbeing. According to the TCM approach, disease results from an imbalance in the flow of the body's vital energy and a disharmony in the interaction of the body with the environment (2). Using herbal medicine therapy, acupuncture, massage therapy (*tui na*), kinesitherapy (*qi gong*), and an adequate dietary therapy (known as the *Five Pillars* of TCM), treatment of disease aims to restore the harmony as well as the flow of vital energy.

During past decades, there is also an increasing interest in TCM in the Western World (3). Patients put hope on TCM as a supposedly "mild" alternative medicine approach, while pharmaceutical research sees the Chinese herbal medicine therapy as a potential source to identify novel active compounds. There is, however, little conceptual overlap between the two approaches, and in contrast to Western medicine, the TCM approach rather resembles a comprehensive philosophy, which is not scientifically verified. There is furthermore a language barrier because existing studies on TCM are often published in Chinese and thus inaccessible to the international research community. Therefore, the Western quest to find their philosopher's stone within TCM has been largely disappointing. In the

Western eye, TCM appears to be a "pseudoscience, with no rational mechanism of action for most of its therapies" (4), and efforts to find new drugs from traditional remedies focused only on one of the *Five Pillars*, the Chinese herbal medicine, disregarding potentially important interactions between different ingredients in traditional therapies (4). Chinese herbal medicine is typically a combination of some 5 to 15 substances, which are often plant or herb extracts but can also be derived from minerals or animal products (1). Safety concerns have been raised regarding the toxicological risks of some ingredients (5) as well as concerns regarding the illegal trade and use of endangered species (6). Furthermore, the effectiveness of Chinese herbal medicine remains poorly researched (2,7). Most of the clinical trials of Chinese herbal medicine had a low methodological quality such as a small sample size or lack of placebo-controlled groups, and a bias toward overestimating the positive effects. This is especially pronounced for studies published in Chinese compared to those published in English (2). With the data available at this time, it is therefore hard to confirm or exclude beneficial effects of Chinese herbal medicine.

In the current issue of *Annals of Translational Medicine*, Lu et al. report about the beneficial effect of Heart-protecting Musk Pills (HMP) in an established model of atherosclerosis, the apolipoprotein E (ApoE) deficient mouse (8), which is prone to develop atherosclerosis on high fat, Western-type diet due to a poor clearance of cholesterol-containing lipoprotein from the blood. HMP are derived from a classical formula in TCM, also known

as Shexiang Baoxin Pills, which dates back to the Song Dynasty (960-1279). They are a widely used in TCM for the treatment of cardiovascular diseases (CVD) including coronary heart disease, heart failure, and hypertension (7). Lu *et al.* have shown that, when administered intragastrically as an aqueous suspension to ApoE deficient mice on Western-type diet, HMP reduced the atherosclerotic plaque burden and thus have an anti-atherosclerotic effect. Mice that received the treatment showed plaques with a thicker fibrous cap and fewer inflammatory macrophages than control mice, indicating an improved plaque stability. Furthermore, the treated mice showed a more beneficial blood lipid profile with reduced levels of triglycerides and low-density lipoprotein (LDL)-cholesterol, but increased levels of high-density lipoprotein (HDL)-cholesterol. This resulted from a profound change in the transcriptional regulation of the hepatic lipid metabolism. The biosynthesis of both cholesterol and fatty acids was downregulated by HMP while cholesterol clearance from the blood via LDL-receptor and fatty acid clearance via β -oxidation was increased. Finally, HMP treatment had a beneficial effect on vascular intimal injury by suppressing apoptosis and increasing NO production in endothelial cells (8).

HMP contain seven different ingredients: Artificial Moschus [i.e., toluene musk, 2-tert-butyl-4-methyl-1,3,5-trinitrobenzene (9)], Borneolum syntheticum [a mixture of optically inactive borneol and isoborneol, prepared from turpentine oil and known in Chinese as synthetic *bing pian* (10)], extracts from Korean white ginseng root [*Panax ginseng* C. A. Meyer (11)], extracts from cinnamon bark [*Cinnamomum cassia* Presl (12)], Storax balsam [a natural resin isolated from the wounded bark of the oriental sweetgum *Liquidambar orientalis* Miller (13)], Venenum Bufonis [a product of the secretions of the Asiatic toad *Bufo gargarizans* Cantor or the Common Malayan Toad *B. melanostictus* Schneider (14)], and Calculus Bovis Artifactus [artificial dried gallstones of cattle, manufactured, among others, from cholic acid, dry bovine bile powder, porcine ursodeoxycholic acid, taurine, bilirubin, and cholesterol (15)]. While some of these substances are chemically well defined, most of them are complex mixtures of different molecules from natural sources, which inevitably rely on individual and seasonal variations. Nevertheless, using gas and liquid chromatography coupled mass spectrometry approaches, several analytical chemistry studies have identified more than 70 non-volatile and 40 volatile compounds in HMP, of which 17 compounds and 4 metabolites were present in the plasma of rats after

HMP administration (7). To understand the mechanism of how HMP work, this knowledge should be used in detailed pharmacodynamics studies of each active ingredient to dissect on the molecular level the anti-atherosclerotic effect that Lu *et al.* have demonstrated here. Which of these molecules has a particular effect on the metabolism of cholesterol in isolated hepatocytes and/or in animal models? Which of these molecules regulates the expression of the LDL-receptor or fatty acid metabolism? Are there possible drug-drug-interactions when combinations of these molecules are tested simultaneously?

Atherosclerosis is one of the underlying causes for the broad spectrum of CVD, including coronary artery disease and myocardial infarction, heart failure, valvular heart disease, hypertension, carotid artery disease and stroke, peripheral artery disease, and chronic kidney disease. CVD is currently the leading cause of death in developed countries, and a pre-eminent health problem worldwide (16). Living standards in China have rapidly improved during the last two decades, and with these dramatic changes in lifestyle, the prevalence and mortality of CVD have significantly increased. Especially in rural areas of China where there is no preventive or primary health care system in place, the mortality rate of CVD has approximately doubled since 1990 (17). It is to expect that particularly in these areas TCM is more commonly used than Western medicine. A profound investigation of the molecular mechanism by which the single active ingredients of HMP exert their anti-atherosclerotic effects will yield invaluable knowledge on their action and potentially dangerous adverse effects.

Interestingly, TCM is often regarded more effective in China for immune conditions, chronic illness, or for diseases of unknown etiology, while Western medicine is regarded more effective in acute situations or for conditions in which the etiology is known (1). Atherosclerosis a complex chronic disorder, which has its origin in an unbalanced metabolic regulation that results in dyslipidemia and accumulation of cholesterol-containing LDL particles on the arterial wall, but the impact of the immune system on the etiopathology of atherosclerosis is not to be underestimated. In fact, atherosclerosis is a chronic inflammatory disease (18). Lu *et al.* have elaborated on the effect of HMP on lipid and cholesterol metabolism in mice, but addressed the immune aspect of atherosclerosis only peripherally. They found that the levels of the proinflammatory cytokines TNF- α , IL-1 β , and IL-6 as well as the acute phase protein CRP were downregulated by HMP treatment (8). Further

investigations of the cellular sources of these marker proteins and the molecular mechanism by which HMP (and their single active ingredients, respectively) affect their levels are needed. In addition, HMP were previously shown to exert anti-inflammatory effects via decreasing the expression and activation of the transcription factor NF- κ B and subsequent suppression of pro-inflammatory bioactive lipid mediators, such as PGE₂ and 12(S)-HETE (7). These bioactive lipids play an eminent role in the development of atherosclerosis (19), but are also important in related detrimental metabolic conditions such as obesity (20).

The discovery of the TCM remedy *qing hao su*, an organic extract from the leaves of sweet wormwood [*Artemisia annua*] with effects against the cause of malaria, *Plasmodium falciparum*, and the subsequent development of its artemisinin derivatives (21), which are presently the most potent anti-malaria drugs and have saved millions of lives, is a prime example of how scientific and traditional knowledge from East and West can be combined for the “greatest benefit to humankind”. This discovery yielded the 2015 Nobel Prize in Physiology or Medicine to Tu Youyou, the first Chinese Nobel laureate in Physiology or Medicine. Repeating such a success story in the cardiovascular field would be a great step forward to tackle the progressive epidemic of CVD in China and worldwide.

Acknowledgments

Funding: The authors would like to thank the Professor Nanna Svartz Foundation, the Swedish Heart and Lung Foundation, and the Swedish Research Council for financial support.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Pawelzik SC, Bäck M. Eastern Remedies for Western-type diet induced atherosclerosis. *Ann Transl Med* 2020;8(6):258. doi: 10.21037/atm.2020.03.39