

Management of Chronic Stable Angina: Modern Microbiomedical Research Provides Insights Into Traditional Chinese Medicine Treatments

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This Commentary relates to the article by X. Zhao et al on pages 458–469.

It is not the delicate neurotic person who is prone to angina, but the robust, the vigorous in mind and body, the keen and ambitious man, the indicator of whose engines is always at full speed ahead.

William Osler.

In 2019, the World Health Organization (WHO) published the Global Report on Traditional and Complementary Medicine (T&CM),^{1,2} halfway through the 2014–2023 implementation period of the WHO Traditional Medicine Strategy, launched in 2002. As stated in the 2019 WHO report, “T&CM is an important and often underestimated health resource with many applications, especially in the prevention and management of lifestyle-related chronic diseases, and in meeting the health needs of ageing populations. Many countries are seeking to expand coverage of essential health services at a time when consumer expectations for care are rising, costs are soaring, and most budgets are either stagnant or being reduced.” Indeed, the overall goal of the WHO Traditional Medicine Strategy and of its implementation is to set the ground for creating virtuous, people-centered health systems, where preventive care, on one side, and medicinal curative treatments, on the other, are optimally balanced. The report on the Global Progress in T&CM over the past 20 years was generated thanks to the contribution of 179 WHO Member States. Thus, most of the WHO Member States have acknowledged the use of T&CM to the point that “by 2018, 98 Member States had developed national policies on T&CM, 109 had launched national laws or regulations on T&CM, and 124 had implemented regulations on herbal medicines.”¹

Evidently, T&CM can contribute to the universal health coverage (UHC) goal by being included in the delivery of essential health services, which perfectly aligns with the 2019–2023 WHO’s 13th General Program of Work that has the primary goal of reaching 3 billion people “to achieve the Sustainable Development Goal 3 (SDG 3)—ensuring healthy lives and promoting well-being for all at all ages—by achieving universal health coverage (UHC), addressing health emergencies, and promoting healthier populations.” However, in order to promote the correct use of T&CM, it is not only important to develop and provide international standards, technical guidelines, and methodologies, but also to use the technological tools currently available to deepen our understanding of the effects of T&CM treatments, typically when used in combination with Western medicine (WM).³

Currently, the deadliest threats to global health include: (1) noncommunicable diseases, such as heart disease, stroke, cancer, chronic respiratory diseases, and diabetes; (2) infections—such as pneumonia, tuberculosis, gonorrhea, and enteritis—that are becoming extremely difficult to eradicate because microorganisms have become resistant to many

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antimicrobials and this leads to prolonged stays in the hospital and higher medical costs; and (3) opioid addiction, because of the raise and misuse of prescription of opioid analgesics for chronic and acute pain with increasing public health risks.

The pilot study by Zhao et al entitled “Effect of DLT-SML in chronic stable angina via ameliorating inflammation, correcting dyslipidemia, and regulating gut microbiota,” hereby presented, provides a compelling example of the integrative use of T&CM and the improvement in patients with chronic stable angina (CSA) treated with WM (Fig. 1).^{4,5} The Dan-Lou tablet (DLT), approved by China Food and Drug Administration to treat coronary atherosclerosis, was already reported to inhibit inflammation and reduce the serum lipid levels. Injections of *Salvia miltiorrhiza* ligustrazine (SML) are also used as a routine treatment for CSA in combination with other medications in the treatment of coronary atherosclerosis. The major chemical constituents are as follows: tanshinone IIA, puerarin, formononetin, paeoniflorin, cryptotanshinone in DLT, and danshensu and ligustrazine hydrochloride in SML. According to previous study and drug instructions, tanshinone IIA and puerarin were formulated for injection.⁶

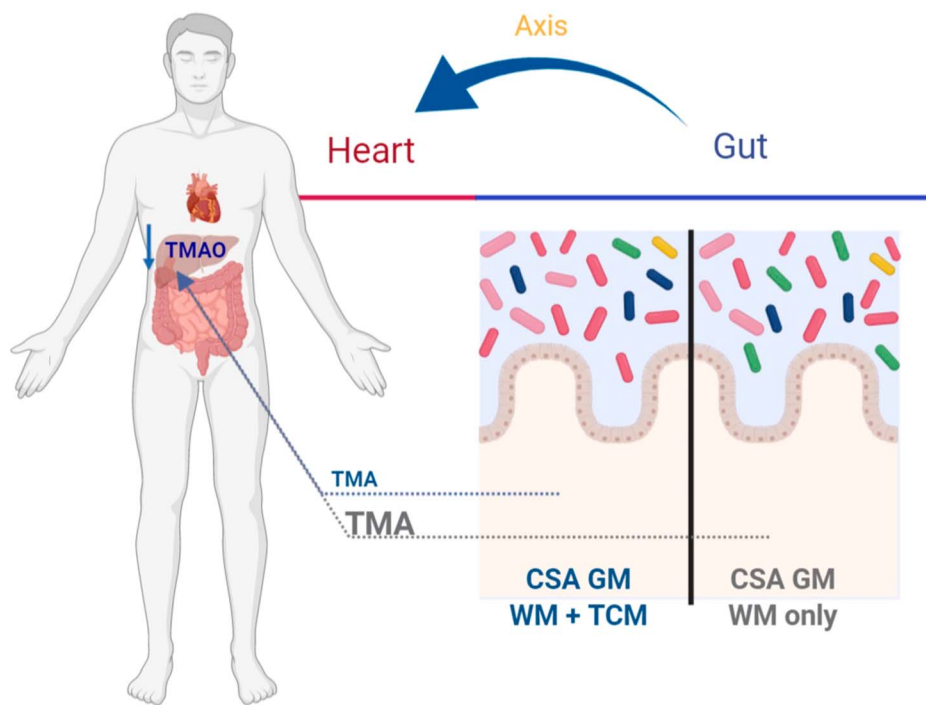
The decision to investigate the effects of the DLT-SML combination was driven by the fact that this is used on patients with CSA in a rural hospital in Heilongjiang province, a region in northeast China; the combination is used for 2 weeks before the sudden arrival of cold weather to prevent winter peaks in cardiovascular events and has the claimed effect of leading to significantly low mortality in patients with CSA. The effects of the application of the DLT-SML combination in the treatment of CSA was studied by Zhao et al for the first time, with the aim of unveiling the

largely unknown mechanisms of DLT-SML combined treatment. The authors also recall that in the clinical perspective sulfotanshinone sodium injection and puerarin injection in combination with WM exhibit significant reduction in the incidence of angina pectoris. Indeed, during their study, Zhao et al did not interrupt the treatment with antianginal therapies. Moreover, and in line with the UHC goal, an added value of this study is that it was performed on patients with CSA treated in a rural hospital in China supported by the New-type Rural Cooperative Medical System.⁷

An interesting outcome of the study by Zhao et al is that after the 2 weeks of DLT-SML treatment the gut microbiota (GM) composition resembled much more that of the healthy control group (HCG) and was significantly different from the GM composition pretreatment. After DLT-SML treatment, the relative abundance of bacterial phylum Firmicutes increased, whereas that of Proteobacteria decreased, although in the high total cholesterol group (16 patients with CSA) the phylum Bacteroidetes well exceeded that of the HCG and of the group with normal total cholesterol (14 patients with CSA).

A further demonstration of the “normalization” in both the composition and the diversity of the GM is provided by the striking (50%) decrease of trimethylamine N-oxide (TMAO) blood levels in patients with CSA after the 2 weeks DLT-SML treatment. TMAO has been recognized as a canonical GM metabolite and its increase in blood levels as a marker of a “dysbiotic state”, ie, a marker of the perturbation in terms of composition and diversity of the distal GM. Diet, stress, antibiotic exposure, infections, pathological conditions, and other factors, alone or in combination, contribute to the establishment of the dysbiotic state; the

FIGURE 1. Gut–heart axis and the management of chronic stable angina by integrating Western medicine with traditional Chinese medicine (TCM). A Dan-Lou tablet-Salvia miltiorrhiza ligustrazine treatment of 2 weeks leads to changes in the composition and diversity of the distal gut microbiota. The treatment causes an increase of the bacteria belonging to the phyla Firmicutes (pink-red) and Bacteroidetes (blue) and a substantial decrease of the phylum Proteobacteria (green), whereas the phylum Actinobacteria is shown in yellow. The observed decrease of the circulating levels of trimethylamine N-oxide (TMAO) is the likely consequence of the decrease in trimethylamine (TMA) levels of GM origin. TMAO is regarded as a molecule responsible for the increase of cardiovascular pathological events. Created with BioRender.com.



outcome is a pathological state and an alteration of circulating GM-produced metabolites. In particular, 2 recent systematic reviews and a meta-analysis of prospective studies strongly support the notion that the increase of the blood concentrations of TMAO (and its precursor trimethylamine, TMA) is associated with increased risks of major adverse cardiovascular events and mortality.^{8,9} The distal GM metabolic activity of L-carnitine, choline, betaine, and lecithin, in particular from undigested red and white meat, fish, and eggs leads to the formation of TMA, which is then released into the bloodstream and reaches the liver. In this organ, a flavin-dependent monooxygenase oxidizes TMA into TMAO, which is regarded as the “bad molecule,” responsible for the increase of cardiovascular pathological events caused by the accumulation of cholesterol in macrophages and of foamy cells in the walls of the arteries,^{10,11} an altered calcium signaling that causes platelet hyperactivity and prothrombotic phenotype in vivo, in addition to a proinflammatory response and alteration of cholesterol metabolism. Several studies are contributing to our understanding of the specific contribution of GM at the genus and species level in the effective control of cardiovascular diseases. The study by Zhao et al confirms that the normalization of the GM is also accompanied by a substantial decrease of proinflammatory cytokines interleukin-1 β and tumor necrosis factor- α , even below HCG levels. It is not unreasonable to explain the observed decrease of cytokines levels and the improvement in the lipid balance as the direct consequence of the improvement in composition and diversity of the GM.

An intriguing finding of the work by Zhao et al also relates to the lower Firmicutes/Bacteroidetes ratio only in the CSA group with high cholesterol. It is tempting to speculate that depending on the cholesterol unbalance in patients with CSA the DLT-SML treatment helps in shaping the GM composition to trigger microbial cholesterol metabolism and a reduction of its circulating levels.¹² Furthermore, a recent report on the destruction of the anaerobic GM in relation to stroke and poststroke infections reinforces the predictive diagnostic importance of circulating GM metabolites in the blood, including that of TMA and TMAO.¹³ Additional studies are warranted to clarify whether the link to dysbiosis, and thus the increase/decrease in the concentration of GM metabolites in patient's blood, has a casual or bidirectional link with the cardiovascular pathological conditions and this holds even truer in the coronavirus-associated disease 2019 (COVID-19) era.^{14,15} Similarly, longitudinal cohort analyses are clearly needed to establish if the pathological condition is triggered by a dysbiotic state or the latter is the consequence of the

pathological condition, but a contributing factor to its worsening. Either way, cutting-edge microbiomedical research will surely greatly contribute to our understanding of these pathological conditions and the best preventive and curative interventions by medical treatment, including when these involve T&CM.

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