

Is there a role for botanical medicines in the twenty-first century?

Promotion of untested traditional therapies by the World Health Organization and China endangers global public health

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Most people worldwide have limited access to science-based health care, receiving primary care from healers who dispense botanical remedies. In Western countries, consumption of alternative medicines, including herbal remedies, has become increasingly popular. The use of botanical products for medicinal purposes is indeed plausible as many medications in current use—digitalis, taxol, and morphine, to name just a few—were originally derived from plant extracts. Artemisinin, an important antimalarial drug, was identified by large-scale screening and testing of plant extracts ordered by Chairman Mao Zedong to address the prevalence of malaria in the Chinese army. Isolation of *qinghausau*, the active principle of *Artemisia annua*, was followed by the application of modern methods: efficient extraction procedures, pharmacokinetic studies in mice, and synthesis of chemical derivatives (Klayman, 1985). Tu Youyou, a Chinese scientist, was awarded half of the 2015 Nobel Prize for Physiology and Medicine for this important discovery.

To ensure the efficacy and safety of prescription medications, the US Food and Drug Administration (FDA), and the European Medicine Agency (EMA) require testing in randomized, controlled clinical trials. However, in English publications, there is, however, little evidence for efficacy among traditional herbal remedies. Indeed, rigorous, placebo-controlled, double-blind clinical trials of eight popular herbals, funded by the NIH, found no benefit beyond a placebo effect, emphasizing the importance of such testing for all medicines (Cohen, 2016).

The longstanding belief that medicines derived from natural products are safe has been refuted by numerous reports of adverse effects associated with herbal remedies. For example, herbals that contain *Aristolochia* plants cause aristolochic acid nephropathy (AAN), a disease entity manifested by chronic kidney disease and cancer of the upper urothelial tract (Nortier *et al*, 2000). Tens of millions of people in Asia and elsewhere who have consumed *Aristolochia* extracts remain at risk of developing AAN (Grollman & Marcus, 2016). The unique mutational signature for aristolochic acid, the toxic principle of *Aristolochia sp*, has been detected in other human cancers, including hepatocarcinoma (Ng *et al*, 2017).

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In Asia and Africa, traditional herbal remedies were reported to cause liver and kidney damage. In one case series, 34% of 103 patients died following admission to a hospital in South Africa after taking traditional folk remedies. A review of hepatotoxicity recorded 111 different herbs or herbal mixtures used in Traditional Chinese Medicine (TCM) thought to cause liver disease (Teschke *et al*, 2014). However, the

identities of plants causing illnesses are generally unknown, in part because native healers are reluctant to reveal the composition of their remedies. Moreover, many commercial herbal remedies, including many that are sold in the United States, are of poor quality and frequently associated with adverse effects (Marcus, 2016). Thus, the widespread usage of herbal medicines of unknown safety and efficacy has become a global public health problem. Here, we discuss recent actions taken by the WHO and by the People’s Republic of China to promote wider usage of traditional medicines. We analyze also societal obstacles to the provision of science-based health care.

World Health Organization

In 1991, the WHO formulated a policy concerning traditional medicines. It also published a series of monographs endorsing their use. The latest of these (World Health Organization, 2013) advocates “the safe and effective use of traditional and complementary medicine”, ignoring evidence of herbal toxicities, even for *Aristolochia* herbs. WHO’s advocacy for herbal remedies is informed by its Department of Traditional and Alternative Therapies, established in 2002. The WHO acknowledged financial support from the governments of China and Hong Kong and from the WHO Collaborating Center for Traditional Medicine in Hong Kong, for developing and printing their latest monograph. China also provided funding for a supplement in *Science* magazine that praised the benefits of traditional

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Chinese medicine. The supplement was formally endorsed in a forward by Margaret Chan who, at that time, was Secretary-General of the WHO.

The International Statistical Classification of Diseases and Related Health Problems (ICD) codes are created and maintained by the WHO. These codes are used worldwide to classify medical diagnoses and for analyzing health trends and statistics. ICD statistics are the basis of important healthcare decisions and are used by healthcare providers for billing insurance companies and health agencies for their services.

A new version of the codes, ICD-11, approved by the WHO assembly in 2019, is scheduled to become active in 2021. It includes, for the first time, TCM and alternative medicine diagnoses designed to facilitate integration of traditional therapies into Western biomedical health care (Cyranski, 2018). In countries that choose to adopt the new codes, healers and practitioners of alternative medicine could bill governments and insurance companies for their services. Given the lack of evidence for the efficacy and safety of TCM, its inclusion in the ICD-11 has been criticized by multiple sources, including the European Academies Science and Advisory Council (EASAC) and the Federation of European Academies of Medicine (FEAM).

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The true impact of the reliance on traditional medicines remains unknown, largely because no system is in place for reporting adverse events, and affected individuals may choose not to seek treatment in clinics or hospitals. In Africa and Asia, the limited information available concerning adverse events derives largely from case reports. Importantly, reliance on traditional herbal medicines discourages patients with treatable conditions, such as diabetes, hypertension, or cancer, from seeking timely diagnosis and treatment.

With its unqualified endorsement of traditional medicines, the WHO apparently has ignored its mission statement, namely

“...to establish and stimulate the establishment of international standards for biological, pharmaceutical, and similar products”. Rather than adhering to international evidence-based standards, implementation of ICD-11 will confer legitimacy on unproven and potentially dangerous therapies, adding substantially to the burgeoning costs of health care.

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China and TCM

Traditional Chinese Medicine’s multifaceted therapies include herbals, acupuncture, cupping, moxibustion, exercise, and diets. In 2016, China’s State Council Information Office issued a 15-year strategic plan for the expansion of TCM to give it equal status with Western medicine (<http://en.people.cn/n3/2016/1206/c90000-9151245.html>). President Xi Jinping also announced his intention to provide China’s large population universal access to health care by 2021.

The goals of China’s strategic plan include creating 300 TCM centers worldwide and increasing sales of traditional herbal medicines. China has already established overseas TCM centers in more than two dozen cities. Current sales of herbal remedies are estimated to be approximately US \$40 billion annually, approximately one-third of China’s US\$117 billion total pharmaceutical market. To facilitate marketing, regulations have been eased. Since 2018, herbal medicines no longer are required to undergo safety and efficacy trials in humans, as long as they are prepared according to classic formulations. Additionally, students of traditional medicine no longer need to pass national examinations that require knowledge of Western medicine.

Traditional Chinese Medicine and herbal dietary supplements produced in China and marketed worldwide have not been tested for efficacy. Moreover, in light of the serious

adverse effects of some herbal remedies, the promotion of TCM as a safe and effective alternative to western medicine is of concern. Half of all drug-induced liver injury in China appears to be linked to herbal medicines; at least 290,000 annual adverse events in China are attributed to their use. Additionally, TCM lacks rigorous quality control. Sequencing of 15 TCM preparations sold in Australia revealed that more than half of these samples contained DNA from animals not listed on the labels, including several endangered species. DNA from *Aristolochia* was detected in four of these samples.

Societal factors

During the past 75 years, there has been remarkable progress in our knowledge of human physiology and of the pathogenesis, prevention, and treatment of disease. As a result, the average life span for newborns has more than doubled during the past century. Nevertheless, the popularity of potentially toxic herbal remedies presents an important problem for public health. Resolving this problem requires identifying and addressing the underlying factors involved.

“The WHO’s association with medicines that are not properly tested and could even be harmful is unacceptable for the body that has the greatest responsibility and power to protect human health.”

Approximately 88% of nations in UN General Assembly have limited biomedical-based health networks owing to a lack of financial resources. Additional factors include deeply rooted cultural beliefs, national pride in traditional medicine, a large market for herbal remedies, and misinformation regarding their effects. In some countries, the use of traditional medicine is fostered by suspicion of imported, “unnatural” medicines. For example, a 2019 survey of malaria patients in Ghana revealed that most Ghanaians preferred treatment with local herbal remedies rather than with readily available Western medications.

Rejection of science has also been a problem in countries with robust science-based

Further reading**Toxicities of herbal medicines**

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health care. Underlying causes include a long tradition of folk healing, promotion of

alternative therapies by celebrities and media personalities, distrust of science, government, and the medical establishment, inadequate regulation of over-the-counter medications, and persuasive advertising by purveyors of bogus treatments.

The WHO plays a vital role in alerting nations to infectious diseases, and in organizing and coordinating responses to epidemics worldwide. It therefore has both the responsibility and the influence to uphold standards for health care, not the least through its ICD codes. Unfortunately, the WHO has not adopted evidence-based standards for promoting folk and alternative therapies. A *Nature* editorial commented that “the WHO’s association with medicines that are not properly tested and could even be harmful is unacceptable for the body that has the greatest responsibility and power to protect human health”.

Remedial actions

What actions could be taken to reduce harm associated with traditional herbal remedies and to make science-based health care more widely available? Foundations that provide approximately 75% of WHO’s budget should insist that WHO provide science- and evidence-based health recommendations. Those foundations could also provide additional support and technical assistance for expanding science-based health networks in countries with limited financial resources.

Limiting the adverse effects of traditional remedies will first and foremost require informing the public about their hazards and overcoming opposition to evidence-based medicines and Western health care. This will require engagement with healers and enlisting their cooperation. Foundations and philanthropies operating in those regions should participate in establishing trust in such new initiatives.

In developed nations, scientists should speak out to educate the public with respect to evidence-based health care. Consumer groups and scientists also should advocate for more oversight of herbal and over-the-

counter medications. Predictably, this message will be resisted on ideological and cultural grounds and by commercial vested interests. Progress will be slow, but it is imperative to start and to improve the safety of all medicines.

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