



## Editorial

# Herbal Cardiotoxicity: Can Mother Nature Hurt the Heart?

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**See article by Zhao et al., pages 395.e5-395.e6 of this issue.**

In the “Wild West” of the 1800s, there was no infrastructure to police the increasingly widespread peddling of “snake oils.” Although some had genuine medicinal benefits, frequently they were solutions of herbal or mineral compounds in various alcohols with the potential to cause toxicity or even death. Problems with this brisk commerce motivated the formation of the US Food and Drug Administration (FDA) under the Pure Food and Drug Act of 1906. This act made it illegal to manufacture misbranded, poisonous, or adulterated remedies. Over the next 3 decades, the FDA’s scope of authority matured, and in 1938 the Federal Food, Drug, and Cosmetic Act finally decreed that commercial remedies must provide scientific evidence of safety. However, it was not until 1962 that the Drug Efficacy Amendment finally introduced a requirement that pharmaceutical manufacturers submit rigorous proof of effectiveness to attain drug approval.<sup>1</sup> Meanwhile, the alternative remedies industry successfully lobbied to limit the FDA’s ability to regulate their products through the passing of the 1976 Proxmire Amendment and the 1994 Dietary Supplement Health and Education Act.<sup>2</sup>

The advent of stricter FDA controls on pharmaceutical companies ushered in a “golden age” of scientifically regulated medication development that provided unprecedented safety and efficacy to patients. As a result, the use of pharmaceuticals rapidly became more widespread. The public also became more aware of an incontrovertible fact about drugs: compounds potent enough to alter the manifestations of disease are also potent enough to cause adverse effects. Wide publication of possible adverse effects makes the practice of medicine safer, but also provides excellent fodder for sensational media coverage and drives profit for legal firms. One has only to look at the multi-million dollar settlements paid by manufacturers of new anticoagulants, despite their being scientifically proved to be safer than older alternatives.<sup>3</sup> As a consequence, pharmaceutical companies protect themselves from litigation by publishing exhaustive lists of rare adverse

effects to ward off claims of uninformed damages. Consumers are left with a confusing and impenetrable wall of medicolegal warnings that has caused an important segment of the public to lose faith in Western medicine. Many patients turn to therapy that they feel Mother Nature has endorsed as safe, products around which unregulated commerce is booming.

However, not all products of Mother Nature are free of harm. The case report by Zhao et al.<sup>4</sup> in this issue of the *Canadian Journal of Cardiology* reminds us that digitalis is not the only naturally derived substance that can cause potentially lethal ventricular tachyarrhythmias, including bidirectional ventricular tachycardia. The report also demonstrates the human tendency to think that if a little is good, more must be better. It is especially tempting to increase the dose of a low-potency alternative remedy to speed or augment its effects. Fu Zi is an anti-inflammatory and analgesic herbal remedy widely used in southwest China. The middle-aged woman who experienced a refractory arrhythmia in Zhao et al.’s report took a large dose of Fu Zi, likely in the hope of better achieving its desired anti-inflammatory effects. The active ingredient in Fu Zi, aconitine, prevents sodium channel inactivation and thus produces a classic experimental model of ventricular tachyarrhythmia at toxic doses.<sup>5</sup> In practicing self-directed therapy, this woman had no advice on how to take it safely, no certainty regarding the accuracy with which the active ingredients were extracted from *Aconitum carmichaeli*, and no assurance that the preparation was not adulterated with other substances.<sup>6</sup>

What should resonate among readers is that patients all over the world are exposed to a wide variety of naturally derived compounds that can be detrimental to their health. These compounds pose a perplexing problem for many clinicians because they are outside their normal scope of Western medicine. For the purposes of this discussion, we can group them under the term “alternative remedies.”

Defining alternative remedies is an imprecise exercise, but they could encompass any health remedy purchased without a prescription. This would include entities described as natural health products or supplements, folk remedies, traditional medicine, Eastern/Asian/Chinese medicine, or complementary medicine. Over-the-counter medications used outside their recommended fashion could also fit the bill. It should be recognized that what alternative remedies share in common

Received for publication August 21, 2015. Accepted August 24, 2015.

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See page 293 for disclosure information.

are seemingly magical promises of benefits despite little or no rigorous proof of efficacy or even safety.

Zhao et al.'s report serves as a timely illustration that alternative remedies do have implications for the practice of cardiology that cannot be ignored.<sup>4</sup> Clinicians need to be aware of what their patients are taking and be prepared to discuss alternative remedies, at least at a basic level. So where can we turn to for guidance? The Internet is a multi-billion dollar gold mine for commerce in alternative remedies. It should also be a treasure trove of advice on how to counsel patients, but what little can be found is mainly directed toward pharmacists and the lay press.<sup>7</sup> Nonetheless, the following is a brief summary of some points to keep in mind when discussing alternative remedies with patients.<sup>8</sup>

Despite the fact that up to 70% of pharmaceutical products are derived from natural substances, one cannot assume that the natural source was safer. Refining natural products into pharmaceutical grade medications is done to improve efficacy and reduce adverse effects. For example, salicylate derived from willow bark provides anti-inflammatory effects. However, when salicylates are consumed in the multigram quantities required to reliably treat arthritis pain, severe gastrointestinal irritation becomes a limiting factor. In response, acetylsalicylic acid (ASA) was synthesized to improve the ratio of anti-inflammatory benefit to gastrointestinal irritation.<sup>9</sup> Similarly, the synthesis of derivatives of desiccated thyroid and the digitalis compounds in foxglove allows accurate clinical titration, which is impossible with natural products of unsure potency. It is paradoxical that proponents of alternative remedies should perceive ASA as less safe than natural salicylate and suggest that naturally sourced compounds would be preferable to their pharmaceutical derivatives.<sup>10</sup>

Since there is no legislation mandating proof of efficacy for alternative remedies, there is little published science about them. However, alternative remedies present problems in 3 areas: (1) pharmacokinetic interactions; (2) inconsistency of potency and lack of information about their constituent components, including possible pharmaceutical additives; and (3) possible adulteration with compounds like heavy metals to increase their selling weight.<sup>11</sup>

Our understanding of the complex mammalian systems involved in absorption, metabolism, and excretion of exogenous compounds is still in its infancy. Yet we already know that the interplay of genetic variation and exposure to plant extracts and drugs can have profound effects on how pharmaceuticals are handled by numerous transport proteins and metabolic enzymes. Ginseng, ginkgo, black cohosh, and St. John's wort are all known to interact with these transporter and metabolic systems, affecting gut absorption and motility, and diluting or binding prescription drugs like anticoagulants and statins. The effects of alternative remedies may also work in opposition to prescribed medications, eg, yohimbe-stimulated tachycardia counteracting  $\beta$ -blockers and vitamin K in green tea producing variability in warfarin effect.<sup>12-14</sup> It is hard enough to study how the known quantities of purified compounds in pharmaceutical products affect the human organism, but the random mixtures of natural compounds found in alternative remedies present a whole other jigsaw puzzle. The fact that alternative remedies so seldom cause disastrous effects is a testament to the resilience of the human organism and the wisdom of using the low potency inherent in unpurified medications.

Unfortunately, like the pharmaceutical industry, the sale of alternative remedies is also a profit-driven business. The same human greed attributed to the pharmaceutical industry can influence manufacturers of alternative remedies to add pharmaceutical agents to their products to increase effectiveness or adulterants to increase profits.<sup>11</sup> The absence of regulatory supervision of the manufacture of natural products greatly reduces costs. Yet the retail price tag of alternative remedies can still approach that of the pharmaceutical products they are purported to replace.

Nephrology, hepatology, and internal medicine disciplines have published studies addressing problems encountered with alternative remedies for some time, but the field of cardiology has lagged behind, perhaps because the noncardiac organs that filter and clean our blood are at greatest risk when alternative remedies go wrong. However, this case of Fu Zi intoxication points out that the heart can also be involved. Having seen a patient die of renal failure after receiving an herbal "cancer cure," I am personally sensitized to the potential severity of alternative remedy-induced toxicity.<sup>15</sup>

Although the sheer number of products available makes it impossible to develop an in-depth knowledge of all the remedies your patients might take, every clinician needs an approach to dealing with them. Here are some suggestions:

1. Always ask if there is *anything* your patients are taking for their health outside of what is on their prescription list. Patients seldom volunteer information about alternative remedies, thinking that herbal compounds and nutritional supplements have no bearing on their care.
2. Provide a sympathetic and nonjudgmental ear. The fact that patients are discussing this with you implies a level of trust and value of your opinion on alternative remedies.
3. Find out the patient's motivation for taking alternative remedies and whether he or she is adhering to a recommended small daily dose or taking large doses.
4. Do not claim knowledge you do not have, but talk common sense. Ask about their evidence that these remedies work. Point out that anecdotes are the best way to market a placebo.
5. Emphasize that Western medicine has its roots in natural medications. Remind them that many pharmaceuticals are molecules derived from nature, but made safer and more predictable by standardizing their strength, controlling quality, and providing scientific study of their safety and efficacy.
6. Although approved pharmaceutical products are not 100% safe, the fact that their adverse effects are publicized does not make them dangerous, only easier to monitor. Lack of regulation, controlled study, and publication of adverse effects does not make alternative remedies safer. It does leave them open to the risk of adulteration with unknown substances, including the very mainstream pharmaceuticals they may be seeking to avoid.
7. Get to know half a dozen of the alternative remedies commonly used in your area of practice. That way you can provide examples of how they might affect the absorption, metabolism, or beneficial effects of the pharmaceutical agents that you are prescribing.
8. Point out that any compound capable of producing beneficial effects must be pharmacologically active and,

therefore, in high enough concentrations could also cause adverse effects. In other words, there is no “free lunch.” Even if a product really were a miracle cure in 1 person, every patient is different, and it could be ineffective or cause harm in another.

9. Ask is the patient getting their money’s worth? When carefully studied, even common vitamin supplements have not been able to demonstrate long-term benefits.<sup>16</sup>
10. Gently discuss whether, if there is no concrete demonstration of benefit, it might be better to stop spending their time and money taking alternative remedies.

In summary, talking to our patients about alternative remedies is our best tool to help protect them. In-depth knowledge of remedies outside your practice is not necessary to have a conversation that can put alternative remedies in perspective for your patient. Avoid claiming complete ignorance to dodge any discussion of alternative remedies. This can only lend credibility to any patient suspicions that as a practitioner of Western medicine, you have been denied the secrets of alternative remedies or are hiding them for ulterior motives. Take the time to deliver a positive therapeutic message about the benefits of the medications you are prescribing; they will work better. None of the medical specialties can avoid encounters with alternative remedies. Now is the time for the discipline of cardiology to step up its game and address this evolving aspect of patient care.

## Disclosures

The author has no conflicts of interest to disclose.

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