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REVIEW ARTICLE



Using herbs medically without knowing their composition: are we playing Russian roulette?

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ABSTRACT

Herbal medicine, a form of complementary and alternative medicine (CAM), is used throughout the world, in both developing and developed countries. The ingredients in herbal medicines are not standardized by any regulatory agency. Variability exists in the ingredients as well as in their concentrations. Plant products may become contaminated with bacteria and fungi during storage. Therefore, harm can occur to the kidney, liver, and blood components after ingestion. We encourage scientific studies to identify the active ingredients in herbs and to standardize their concentrations in all herbal preparations. Rigorous studies need to be performed in order to understand the effect of herbal ingredients on different organ systems as well as these substances' interaction with other medications.

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Introduction

"First, do no harm." Hippocrates, 460-355 BCE

Two influential European advisory bodies, namely, the European Academies' Science



Advisory Council and the Federation of European Academies of Medicine recently recommended that herbal medications should be subjected to the same regulatory oversight and the same robust quality standards that are mandatory in conventional Western Medicine¹. As stated in the journal, *Nature*, "Hundreds of years of use in clinics that don't standardize or analyze the clinical data are no match for blinded, controlled studies."²

Three of the authors harbor great interest in herbal medicine as a result of having been born, raised and educated in the Far East and having been exposed to considerable amounts of herbal medications during their youth (even including their times as junior Western-style allopathic medical students). The use of complementary and alternative medicine (CAM) in developing and developed countries alike has been in vogue for the past decades and refers to the application of elements of traditional medicine (TM) practices or any other "natural" or non-conventional forms of treatment. The World Health Organization reported in 2005 that in China, TM accounts for about 40% of all health care and in Africa

80% of the population use TM. The percentage of the population which used CAM at least once was around 40–50% in Belgium, the US and Australia, up to 70% in Canada and 75% in France³. Current goals of the World Health Organization include integrating safely traditional and complementary medicine in health care practices⁴.

The National Health Statistics Reports from the US Centers for Disease Control and Prevention estimated that adults in the US spent \$30.2 billion out-of-pocket in 2012 on both visits to CAM practitioners and purchases of CAM products, and materials⁵. Purchase of non-vitamin and non-mineral "natural" products represented about 40% of all out-of-pocket costs for CAM. Interestingly, the costs for these products were more than twice that reported a decade earlier, indicating the growing utilization of CAM⁶. In the US, females, college graduates, and those who considered the quality of their healthcare to be poor were more likely to use CAM, whereas African-Americans were less likely to use CAM. Among CAM users, 47.6% did not inform their doctors about such use⁷.

Much has been written about the fallacy and risks of CAM, particularly when insufficient scientific evidence exists to support its efficacy for a particular disease. Yet countless numbers of well-educated and apparently reasonable people continue to regard CAM as the first line of defense against major illnesses. The very thought of receiving something

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“natural” seems to have the unique capacity to mesmerize people and cloud their judgment. This is especially enhanced when faced with the alternative avenue of treatment, the allopathic approach, that has well-publicized known side effects and complications.

The quality of preparation of herbal medicines varies. Although nowadays some herbal medicines are manufactured in the form of capsules, powders or tablets, in the Far East, the majority of these medicines have traditionally been concocted by boiling a host of plant ingredients, usually ending up in a bowl of blackish-brown, thick and bitter liquid referred to as “bitter tea” by some children (personal experience of Asian co-authors of the present communication). There is no consideration for age, sex, race, body weight, body composition, genetics, and organ [e.g. liver, kidney, and blood] functions (observed by the Asian co-authors of the present communication before and after they had completed their medical training). Plant parts such as leaves, flowers, fruits, stems, branches, and roots may be included in the concoctions and occasionally animal products as well. The exact ingredients and their concentration in the final mixture are generally unknown, not only to the prescriber but also to the consumer. Moreover, whether the sundry ingredients of the final concoction might present adverse interactions with one another inside the body after consumption is entirely unclear. The composition of plant ingredients varies immensely with environmental factors, such as the season, rain or snow fall, irrigation, amount of sunshine, temperature variability, chemical contamination (in the form of fertilizers, insecticides, pesticides, herbicides, heavy metals, etc.), and other soil problems. Recently, the process of horizontal transfer was discovered where alkaloids leached out from decomposing or living donor plants are taken up by the roots of accepting plants and can be modified in the acceptor plants by hydroxylation and/or glycosylation resulting in contamination of the plant of interest⁸. Additional variables include the genes and health of the plant, and the part of the plant that is being used. The skill of the persons collecting the plant material, their ability to distinguish the desired plant from similar-looking (sometimes toxic) plants and storage conditions of the collected organic material contribute to the overall crucial concerns. Improper storage may promote bacterial and fungal contamination. The exact detail of preparing the mixture such as the temperature during its preparation, drying or boiling and the volume of diluent added are unknown. An example of the importance of the temperature factor can be seen in the extraction of artemisinin when a high temperature could destroy this ingredient from the parent plant, *Artemisia annua* (also known as sweet wormwood)^{9,10}. Even under controlled production in the pharmaceutical industry harmful contaminants of N-methylnitrosobutyric acid and N-nitrosodimethylamine were detected in losartan and ranitidine-containing products respectively¹¹. Those contaminants were discovered only through repeated monitoring and testing. Danger is posed by the undesirable elements lurking within poorly studied herbal and alternative medicines whose exact composition remains largely unknown. It is not

an exaggeration to say that when one takes sundry herbal medicines, one is playing a game of Russian roulette. “First, do no harm” should apply to all medications, allopathic or herbal.

In this report, we review briefly the herbal origin of established life-saving drugs, and present examples for the damage to body organ systems caused by the use of certain herbal medicines. We review the current status of research on the efficacy and safety of herbal medicines for various disease states, mainly focused on kidney, liver and blood injury, and discuss future developments required for integration of beneficial herbal ingredients into health care systems. Our main addition to the existing literature is to argue that herbal products need to be regulated in the fashion applied to the regulation of drugs produced in chemical laboratories.

Pathophysiological consequences

Plants have provided useful medicinal treasures that immensely benefited humankind over the millennium. Classic examples include vitamin C from citrus fruits, salicylates from the bark of a willow tree (*Salix alba*), quinine from the bark of the *Cinchona ledgeriana* tree, penicillin from a mold in the form of *Penicillium notatum* or *Penicillium chrysogenum*, digitalis from fox glove, reserpine from *Rauwolfia serpentina* (an Indian plant), ephedrine from *Ephedra sinica* (Ma Huang, a Chinese plant), dicoumarol from moldy sweet clover hay, artemisinin (for the management of malaria) from a shrub categorized as *Artemisia annua* L., paclitaxel derived from the bark of the pacific yew tree *Taxus brevifolia* (for the treatment of certain cancers), to name just a few.

Most herbal products fall under the category of dietary supplements. Congress defined the term “dietary supplement” in the Dietary Supplement Health and Education Act (DSHEA) of 1994. These products are not required to meet the standards and restrictions applied to pharmaceutical drugs in the United States. This is the root cause for many avoidable instances of harm caused by herbal products. Additionally, patients often do not inform their health-care providers about the ingestion of herbal remedies, as was shown in a survey in the United Kingdom¹². As a result, lives have been lost unnecessarily due to the ingestion of herbal medicine¹³.

Renal injury

A nephropathy caused by herbal medications contaminated with aristolochic acid has been referred to as Aristolochic Acid Nephropathy. The disease was first recognized in Belgium amongst individuals who took herbal medicines advertised to promote weight loss but contained aristolochic acid¹⁴. In Taiwan, where the National Health Insurance covers the cost of herbal products, a high incidence of end-stage renal disease exists. Mu Tong and Fangchi, two commonly consumed herbs, were found to be associated with end-stage renal disease and both were discovered to be contaminated with aristolochic acid¹⁵.

The chronic use of herbs was associated with a 20% increased risk of developing chronic kidney disease in Taiwan. Specifically, the proportion of herbal users quantitatively correlated with the severity of renal failure¹⁶. More recently, aristolochic acid, from *Aristolochia clematitis* which grows mingled in the wheat fields of the Balkans was also found to be the long-sought cause of Balkan Nephropathy¹⁷. In addition, myriad other nephrotoxic herbs exist that can result in an array of kidney syndromes, including acute tubular necrosis, interstitial nephritis, proximal or distal tubulopathy, papillary necrosis, nephrolithiasis and urinary retention^{18,19}.

Liver injury

Many herbal medications have been identified to cause liver disorders such as hepatitis (acute, chronic and autoimmune), cholestasis, cirrhosis, vascular lesions and potentially even liver failure. Contaminations with microorganisms, pesticides, heavy metals, synthetic drugs and fungal toxins such as aflatoxin have been reported as the potential reasons²⁰. Quan and co-authors identified two groups of hepatotoxins: the phyto-hepatotoxin group consists of phytochemicals and their metabolites produced naturally in plants, while the non-phyto-hepatotoxin group consists of contaminants or adulterants, e.g. pesticides²¹. Another contaminant, pyrrolizidine alkaloids (PA), has been found in over 6,000 plant species growing in countries all over the world. PAs with a double bond between C1 and C2 structure exhibit strong hepatotoxic, genotoxic, cytotoxic, neurotoxic and tumorigenic potentials. The consumption in error and in large amounts of plants with the 1,2 unsaturated PAs, can lead to severe liver injury by generation of radical metabolites *via* metabolism by the p450 (CYP) system^{22,23}.

Some herbal remedies only cause side effects due to their interaction with other drugs. For example, St. John's wort (*Hypericum perforatum*), used for the treatment of depression, causes hepatotoxicity by interacting with medications such as cyclosporine, simvastatin, warfarin and digoxin *via* the effect on liver enzymes such as cytochrome p450²⁴.

Direct hepatotoxic complications resulting in acute and chronic hepatitis have been described from the use of Jin Bu Huan (*Lycopodium serratum*), a drug employed to produce mild sedation²⁵. Ma Huang, a weight loss product marketed in the United States, caused acute hepatitis with concomitant increase of antinuclear antibodies and smooth muscle antibodies after three weeks of intake. Symptoms resolved after discontinuation of the drug²⁶. Many other reports can be found regarding the hepatotoxic effects of herbal medicine^{27,28}. In the United States, the Drug-Induced Liver Injury Network provides comprehensive data on herbal and dietary supplements-induced hepatotoxicity. It reported that the proportion of liver injury attributed to herbs had been rising over time²⁹.

In recent times, the method of establishing herbal hepatotoxicity was switched from expert opinion to sets of objective criteria. The Roussel Uclaf Causality Assessment Method (RUCAM) was created to establish the presence of Drug-

Induced Liver Injury (DILI)³⁰⁻³². RUCAM assigns points for clinical, biochemical, serological, and radiologic features of liver injury and computes a score indicating the degree of probability – “absent”, “unlikely”, “possible”, “probable”, or “highly probable”- that a liver injury was due to a specific medication³⁰⁻³². This method has been used extensively for the diagnosis of both DILI and Herb-Induced Liver injury (HILI)³³⁻³⁶. In a recent review, Teschke and Danan concluded that RUCAM outperformed other methods in establishing the diagnosis of DILI or HILI³⁶. The prevalence of HILI detected by RUCAM is low. In a prospective study, Melchart and co-investigators reported that only 26 of 21,470 patients (0.12%) who had received traditional Chinese medicine developed HILI that resolved after cessation of the medicine³⁷.

Hematological disorders

Certain traditional herbal remedies cause aplastic anemia³⁸. *Slavia miltiorrhiza*, *Angelica sinensis* and papaya are known to alter coagulation and increase prothrombin time. In a survey taken among patients prescribed warfarin in 35 general practices in the United Kingdom, 8.8% of patients were taking certain herbal remedies known to interact with warfarin. The vast majority of these patients (92.2%) did not discuss the use of herbal remedies with their healthcare providers¹².

The science of herbal medicines

In one of the time-tested approaches in the development of new drugs, folklores are first employed to sort out plants or their components that have been claimed over the years to possess beneficial effects on certain ailments. Vigorous scientific investigations involving laboratory, animal and human studies are then carried out on those plant-derived substances. Once the latter's effectiveness is confirmed, identification of the active ingredient(s) is needed. The active ingredients and/or their derivatives are then subjected to more clinical evaluations. It is only after clinical evaluations have confirmed the efficacy and safety of those ingredients that they should be considered for medicinal use in humans.

This vigorous nature of Western medicine development process ensures that the efficacy and toxicity profile of various therapeutic agents meet pre-set standards. In contrast, the quality of studies on herbal medicine has been far from optimal³⁹. Most clinical studies neglect strident diagnostic and therapeutic criteria, rendering their published results unreliable and unscientific. Besides, many prospective randomized studies do not report several important components of a clinical trial, including sample size calculation, randomization sequence, allocation concealment and intention to treat analysis^{40,41}.

In spite of these shortcomings, however, the merits of herbal medicine should never be underestimated or ignored. The recently published Consolidated Standards for Reporting Trials Statement extension for herbal medicine formulas help establish a framework that will improve the designs and reporting of clinical trials involving herbal medicine^{42,43}. We should fully embrace evidence-based, systematic

examination. Such proper scientific approach was exemplified by the discovery of paclitaxel and artemisinin. Artemisinin was discovered by the Chinese Nobel Laureate Youyou Tu^{9,10}. In 2015, the Nobel Committee emphasized that they had not given the Nobel Prize to traditional Chinese medicine but to a scientist who used modern, sophisticated, scientific, research methods to search for a new therapy for malaria⁴⁴. The process of turning an active component in plants into a modern drug involves laboratory studies and tests on animals and humans, which is significantly different from how the herb has been used in traditional Chinese medicine practice for hundreds of years. The clinical use of artemisinin demonstrates once again the enormous potential of herbal medicine in the modern era^{45,46}.

More randomized clinical trials of better quality have been published, showing beneficial effects of herbal medications in conditions such as diabetes mellitus⁴⁷, hypertension⁴⁸, reduction in proteinuria and renal function decline^{49–51}. A number of meta-analyses published in recent years evaluated the effects of herbal medicine in different medical conditions, including bronchiolitis in infants⁵², psoriasis⁵³, rheumatoid arthritis⁵⁴, and irritable bowel syndrome⁵⁵. While the herbal medicines appear to be safe, the available evidence in the literature does not appear to be sufficient or vigorous enough to confirm their benefits^{53,55}.

Future of herbal medicines

It cannot be overemphasized that many poisons such as arsenic, lead, mercury, curare, cyanide, strychnine, snake venoms, endotoxins, and uranium are “natural” products of our universe too. So being “natural” does not equate or confer safety and effectiveness.

The fact that herbal medicine has been in use for hundreds, if not thousands, of years, does not mean that it is devoid of ill effects as the latter may be subtle, slow-progressing and cumulative. A good example is aristolochic acid-containing herbs which have been in use for many centuries in various countries. Yet, their nephrotoxic and carcinogenic effects on the urinary tract were unearthed only in the latter part of the last century. People might have died unnecessarily as a result of slow-progressing complications from having been exposed singly or repeatedly to the toxic effects of certain herbs. If the duration between exposure and the overt toxicity (including death) is long, this association can be easily overlooked.

The day that science has finally demystified the exact composition of the myriad agents used in herbal medicine will be the day when it is safe to wholeheartedly embrace herbal therapy. The strict criteria of scientific rigor in the determination of the efficacy and side effects of conventional medications must be applied equally to those “natural” preparations¹.

Finally, it is heartening to learn that an array of institutions, located both in the East and in the West (e.g. the U.S., Germany, Taiwan, Belgium, the United Kingdom, Australia, China [including Hong Kong] and others), are marshalling their vigorous efforts to investigate plants and related

products that might be of use in medicine. There are different strengths and weaknesses in both Western and herbal medical practices. A combination of both, theoretically, may optimize patient care as these two streams can complement each other. To achieve this goal, it is essential for the herbal industry to establish methodology for quality control ensuring consistent and standardized products⁵⁶. Recent methodological developments should mitigate the numerous challenges in the process of drug discovery from natural product⁵⁷.

We earnestly look forward to the day when rigorous scientific investigations can assure us which medicinal herbs and/or their derivatives are effective and safe to use. The future of herbal medicine, when pursued in the above fashion, can be very bright indeed.

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Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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