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Phytochemistry and traditional medicine—The revolution continues☆

Geoffrey A. Cordell [a,b,*]

[a] Natural Products, Inc., Evanston, IL, USA
[b] Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL 32601, USA

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ABSTRACT

The use of traditional medicines, phytotherapeuticals, and dietary supplements, should be based on quality, safety, efficacy, and consistency (QSEC). Evidence relating to each of those facets of a plant-based medicine is being hampered, in part, by fourteen myths. While these myths are both powerful and persistent, they must be debunked for significant progress to be made in enhancing integrated global health care. This paper, an update on an earlier report, will examine these myths, and the roles that phytochemistry should play in this process. Some examples of the use of the new strategies will be presented from the contemporary literature, together with a brief summary of a clinical trial of a traditional medicine treatment for obesity, and a summary of activities in the European Union to address issues related to the approval and marketing of traditional Chinese medicine (TCM) products.

1. Introduction

In a previous article in this journal (Cordell, 2011b), a brief summary was presented of the tightly interwoven links between phytochemistry and traditional medicine* (* includes phytotherapeuticals, dietary supplements, and cosmeceuticals) from both a historical and contemporary perspective. Emphasis was placed on the new technologies that were being introduced, particularly barcoding and principal component analysis, and how they were contributing to strengthening the evidence base for enhancing the quality, safety, efficacy, and consistency (QSEC) of traditional medicines in order to place patient expectations on a more assured footing. This brief report will describe some selected developments occurring in traditional medicine from a phytochemical perspective. In the previous report, mention was made of four "myths" associated with traditional medicine which needed to be debunked in order for significant progress to be achieved toward the provision of sustainable, evidence-based traditional medicines in a health care system. Further examination has revealed ten additional myths, for a total of fourteen (so far!). An important question to address is whether any or all of these myths are serving as an intellectual barrier to providing a continuum of evidence of the QSEC of traditional medicines. This paper will examine these myths, and the role that phytochemistry is acquiring in challenging them, and will identify some recent examples of success through consortial developments, and experimental reports the Chinese literature and elsewhere. Areas where additional phytochemical effort is needed will also be discussed. A fundamental underpinning to all chemical and biological studies involving plant-based traditional medicine is appropriate chemical analysis. How effective that analysis is in a given setting will determine, to a large extent, the quality and the consistency of the final product, and therefore the anticipated health benefit for the patient.

1.1. Ethnopharmacology background

As humankind spread, indigenous groups all over the world turned to an abundant, renewable local resource, plants, for healing purposes (Balick and Cox, 1996). Their clinical experimentation,

☆ This paper forms part of a special issue of *Phytochemistry Letters* dedicated to the memory o Andrew Marston (1953–2013), an outstanding phytochemist who is much missed by his friends.

Abbreviations: ADR, adverse drug reaction; CAE, caraway aqueous extract; CBD, convention on biological diversity; CCDS, characteristic components data set; ESI, electrospray ionization; GC, gas chromatography; HPLC, high performance liquid chromatography; LC-IT-TOF-MS, liquid chromatography-ion trap-time-of-flight mass spectrometry; MS, mass spectrometry; NHSQP, Niuhuang Shangqing pill; NMR, nuclear magnetic resonance; PLS-DA, partial least squares-discriminant analysis; QSEC, quality, safety, efficacy, and consistency; SFDA, State Food and Drug Administration; TCM, traditional Chinese medicine; TLC, thin layer chromatography; TM, traditional medicine; TRIPS, trade related aspects of intellectual property rights; UPLC, ultra performance liquid chromatography; WHO, World Health Organization; WPRO, Western Pacific Regional Office; WTO, World Trade Organization.

* Correspondence address: Natural Products, Inc., Evanston, IL, USA.
Tel.: +1 847 903 1886.
E-mail address: pharmacog@gmail.com

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passed on through the centuries, forms the basis of traditional medicine today. Prior to 1899, when aspirin was introduced, it was the only form of drug-based healing; in many parts of the world, for reasons of access, it still is. For those patients, little has changed in thousands of years.

Until the start of the globalization of medicinal plants in the early Sumerian period, and subsequently with the development of the land and sea "Silk Road" passages (Wood, 2002), the medicinal plants used were sourced locally. Today, most medicinal plants in commerce remain locally-derived, and are used based on local traditional medicine practices and customs (Lange, 2004). Indications of the safety and efficacy of these plants, as passed on through generations, came through trial and error – it was classical, low throughput clinical screening.

Over time, locally, regionally, and globally, vast numbers of plants, may be more than 50,000, have been described as possessing useful biological activity (IUCN, 2007; Schippmann et al., 2006). This represents at least 12% of the estimated global wealth of higher plants (Kew, 2014). During these thousands of years a vast amount of information regarding the preparation and use of medicinal plants for the ailments that inflict humankind has been acquired. However, this information describing the possible biological and clinical significance of these plant preparations is extremely widely dispersed. There are no, readily available, regional or global databases which have attempted to cumulate this knowledge. What knowledge has been consolidated is partially available through books, both ancient and new, reports in the primary and secondary literature, and sporadic focused databases in various parts of the world. From an intellectual property perspective, this acquired, albeit crudely organized, information is already in the public domain.

There is also an unknown volume of ethnomedical information being held and used every day by medicine men and women, shamans, curanderos, hakims, dukuns, etc. throughout the world. This indigenous knowledge may or may not be in the public domain, and that which is not, is therefore protected as the intellectual property of the individual or group by the Convention on Biological Diversity (CBD) of 1992, and the subsequent Nagoya Protocol of 2010. It is worth mentioning that only three countries in the world are not signatory parties to the CBD, the United States, Andorra, and the Holy See (Convention on Biological Diversity, 2014). Access to this locally held, ethnopharmacological information, in a manner akin to indigenous bioresources, requires negotiated agreements, and other considerations deemed important by the holders of the knowledge. These issues, together with the relationship to the TRIPS Agreement, which holds an opposite view of what constitutes ownership of intellectual property by indigenous groups, are discussed in detail elsewhere (Cordell, 2010; Union for Ethical Biotrade, 2010).

Whereas human beings have consistently sought to consolidate various aspects of recorded knowledge and make it readily available, sometimes for a price (*Encyclopedia Britannica*), at other times for free (*Wikipedia*), on a global scale, this has not occurred for the knowledge regarding the use of plants for healing purposes. This has occurred even though good health is a core facet of the human existence on a moment to moment basis. Ironically, the astronomical sciences have, over hundreds of years, created preliminary detailed maps of the estimated 176 billion galaxies in the universe (Anonymous, 2012). Thus while maps of the sky and the movements of planets in galaxies abound, there is no database to indicate where the medicinal plants are on Earth, how they are being used in primary health care each day, and what research has already been reported to assure their quality, safety, and efficacy for patients. This is an inexplicable and unconscionable gap in the basic knowledge of human life on Earth.

1.2. R-E-S-P-E-C-T

Ethnopharmacological information, depending on the culture and the relationship to "modern" medicine, and the use of associated plants and practices, may or may not be respected and recognized formally as an active and contributing component within a health care system. In some countries, the two systems of medicine operate under government authority and regulation in parallel. In other countries, traditional medicine is not included as a part of the health care system, and thus is not regulated, or covered by insurance, even though it may be very widely used. It is essentially dismissed at the government, and consequently at the scientific, levels, as being irrelevant in the society. A WHO global survey of the regulations and status of traditional medicine conducted in 2003 (World Health Organization, 2005) provided some interesting insights. Only 141 Member States (74%) provided a completed survey, and of those, only 45 (32%) had a national policy on traditional medicine or complementary and alternative medicine (TM/CAM). With respect to regulations, 53 (37%) countries had laws and regulations governing TM/CAM practices, although 86 (61%) countries had a registration system for traditional medicine products. Seventy-five countries (53%) reported having a national office in charge of TM/CAM. A further WHO survey in underway and results are expected to show a steady improvement. However, even in Member States where TM/CAM is an important aspect of health care, status and investment in enhancing the systems for oversight of products and services is lacking.

Without that respect, and the awareness that traditional medicines have contributed to "modern" medicine significantly in the past 210 years, beginning with the studies on opium, and that these practices are both widespread and medically significant in the global population, the appropriate level of strategic investment will not be available. While this intellectual and fiscal "health care gap" is a very shameful situation which affects most of the people in the world, and needs to be "minded" (Cordell and Colvard, 2012), another aspect of this "failure to appreciate" traditional medicine also affects those who are a little wealthier or even rich; that aspect is polypharmacy. Many patients taking regulated medications in the world, through physician recommendation, or self-medication, concurrently take both "modern" and traditional medicines. This is frequently a "black box" of potential biological responses, a step into the abyss of health care outcomes, particularly with poorly regulated products. With few exceptions (Fugh-Berman, 2000; Shaw et al., 2012; Zhang et al., 2012), the clinical effects of taking both forms of medicine are unknown, and, unless mechanistically defined, not predictable in terms of pharmacokinetics, metabolism, synergy, antagonism, pharmacokinetics, etc. From a modern medical viewpoint, often supported by local medical associations, this situation pertains in many countries because the plants in the complementary or traditional medicines are regarded as innocuous, that they will do no harm. Thus, the more "powerful", "modern" medicine will be the dominant chemical force, and prevail. Under these circumstances of prejudicial thinking, clinically significant adverse events may not be reported. This aspect of traditional medicine usage with respect to healthcare outcomes is also of concern to WHO (World Health Organization, 2004).

The reporting and analysis of these plant drug-drug interactions is known as pharmacovigilance, and is defined as "the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities" (Mann and Andrews, 2007). In addition to plant drug–drug interactions, pharmacovigilance (also known as adverse drug reactions, ADR) includes side effects, reactions due to overdose, tolerance, hypersensitivity, and toxic effects (either inherent in the plant or as a result of adulteration or contamination). It should be readily apparent, from an analytical

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