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Phytochemistry and traditional medicine – A revolution in process

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ABSTRACT

Selected contemporary aspects of the inextricable link between phytochemistry and traditional medicine are discussed. New technologies, including plant barcoding and principal component analysis, are being deployed in the development of strategies to provide an evidence base for the quality, safety and efficacy of traditional medicines, as a route to improved health care. The role of phytochemistry in underpinning this evolving evidence base is explored.

1. Introduction

It is widely considered that the birth of "phytochemistry" was the isolation of tartaric acid from grapes in 1769 by the Swedish chemist Carl Wilhelm Scheele, although Marggraf had isolated sucrose from sugar beets 22 years earlier. The seeds ("arcanum") of biological activity in medicinal plants to which Theophrastus Bombastus von Hohenheim ("Paracelsus") referred in the 15th century, we now call molecules. It was the therapeutic properties of these plants, disclosed by diverse cultures over the millennia, which formed the basis of health care the world over. In early part of the 19th century, one of the challenges was to study these active principles.

The place to start the investigation was obvious; the most powerful, and probably the most notorious, traditional medicine on Earth, opium, *Papaver somniferum* L. The power of opium was legendary. Now, for the first time, the curiosity was unbearable. Some primitive tools to investigate what was inside the plant were available, and some investigators had the courage to test the isolated material on themselves; the pharmacist apprentice Frederich Sertürner did just that with opium, isolating morphine. A dramatic period of exploration followed, resulting in the isolation of the main active ingredients of the most famous traditional medicines of the time, strychnine, emetine, piperine, caffeine, quinine, colchicine, and, in 1826, coniine.

After August Kekulé proposed the linking of carbon atoms in 1858, curiosity shifted to elucidation of the structures of these isolated biological agents. Were they similar in structure, were they different, what atoms did they contain, how were those atoms arranged? How many of these compounds were, as Louis Pasteur had determined for tartaric acid, chiral? Was there a relationship between the structures of the compounds and their biological effect? Many questions, too few answers; for the questions, though straightforward for a simple alkaloid such as coniine, were significantly more challenging for strychnine, whose structure took 127 years of degradative organic chemistry to elucidate. Now, strychnine, in all its structural glory, could be deduced *de novo* through modern 2D nuclear magnetic resonance (NMR) spectroscopic techniques in an afternoon perhaps.

This discussion is offered to make two important points. Firstly, that phytochemistry and traditional medicine are inextricably linked; indeed that it was curiosity about one which led to the development of the other. Secondly, that the technologies now available make it possible to determine the secondary metabolic profile of a plant, at a given point in time, rapidly and in significant detail, and, albeit in a limited manner, correlate that information with biological activity.

Plants are stunning chemical factories, and chemotaxonomy has provided some broad, albeit substantially incomplete, assessments regarding the distribution of various structural classes of secondary metabolites, such as alkaloids, quassinoids, flavonoids, betalains, etc. For example, one would not expect to find a monoterpene indole alkaloid, such as vindoline, in a plant in the

Abbreviations: AFLP, amplified fragment length polymorphism; CBOL, consortium on barcoding of life; CITES, convention on international trade in endangered species; GPS, global positioning system; HPLC–MS, high performance liquid chromatography–mass spectrometry; ISSR, inter-simple sequence repeat; IUPAC, international union of pure and applied chemistry; NAPRALERT, natural products alert; NMR, nuclear magnetic resonance; PCA, principal component analysis; RAPD, random amplified polymorphic DNA; WHO, World Health Organization.

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family Amaryllidaceae, or the Asteraceae, or the Solanaceae, extensive in number and as chemically diverse as those plant families are. However, the period of analyzing plants on that basis, solely for chemotaxonomic purposes, is now largely over. Huge gaps in knowledge remain. For example, it was pointed out (Cordell et al., 2001) that there are over 153 plant families which have never been investigated for the presence of alkaloids, and 35 plant families for which alkaloids have been detected and from which no alkaloids have ever been isolated. Some gaps may subsequently be filled, in part, as genetic information accrues regarding which plants possess which genes for which biosynthetic pathways, even though those secondary metabolic pathways may not always be expressed. It is the chemical profile, and the *potential* chemical profile, which is of considerable significance in terms of biological outcomes and regulatory standardization for a medicinal plant. It is also important to recognize one, neglected, concept in the chemotaxonomic assessment of the chemical profile of a plant. As a digital photograph is a "photographic moment" in time, so the determination of the chemical constituents in a dried plant material is, assuming no degradation of metabolites, a "phytochemical moment" in the dynamic metabolic profile of that plant. It is not a definitive assessment of the secondary metabolite capacity of that plant; a perspective to be mentioned subsequently.

A broad revolution in phytochemistry is strengthening its relevancy through the application of powerful new technologies, and is restoring and enhancing the original link between phytochemistry and traditional medicine. By the end of this brief contribution, at least one aspect of the new raison d'etre for phytochemistry at the very forefront of the rapidly evolving evidence base of traditional medicine, should be evident.

2. The changing face of traditional medicine

The World Health Organization (WHO) (Anonymous, 2002) defines traditional medicine as "...health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illness or maintain well-being". For much of the world, traditional medicine has changed little in the last 4000 years (Cordell, 2007, 2008, 2009, in press-a, in press-b; Cordell and Colvard, 2005, 2007). At the same time, for at least 4.5 billion people on Earth, plant-based traditional medicine is their dominant, or perhaps only, form of accessible primary health care (Payyappallimana, 2010). It represents part of the enormous health care divide in the world between North and South. The issues are substantial and disturbing, but unfortunately cannot be discussed in this context, other than to indicate the vast gulf in infrastructure for studying traditional medicines that exists between the North and the South (Boutayeb, 2007). Many countries of the world now understand that their health care needs as far as drugs are concerned, both for local and global diseases, will not be provided by the dominant pharmaceutical companies (Boutayeb, 2007; Campaign, 2010; Jarvis, 2010; Newman & Cragg, 2007). Those companies are seeking alternative strategies which reduce the scope of investment of their research and drug discovery operations (Jarvis, 2010; Mullin, 2010).

Some countries, such as India, have developed local capacity to produce at least some of the organic chemicals needed for generic pharmaceutical products (Tremblay, 2010), once they are no longer patent protected. Some countries, for example South Africa, have begun to look at their locally available traditional medicines with a view to drug discovery. Other countries, for example China, are developing traditional medicines as a means to drug discovery and to raise the quality of the plant product acquired by the patient as part of the global expansion of traditional Chinese medicine which is now underway. Populations all over the world in lower-income countries though may only have access to local traditional medicines based on plant materials as their critical source of primary health care.

In the past ten years, a significant shift has occurred in the strategic approach to traditional medicine, although that development is not yet fully recognized, or well funded. In some ways, the revolution began with the publication of the *WHO Traditional Medicine Strategy 2002–2005* (Anonymous, 2002). This seminal document elucidated a four-part strategy to improve traditional medicine on a global basis. Development of guidelines for safety, efficacy and quality was regarded as a fundamental requirement in order to establish a solid evidence base for traditional medicine. Much has changed in the years since that document was prepared, and numerous new strategies are now evolving (Cordell, 2008, 2009, in press-a, in press-b). The International Union of Pure and Applied Chemistry (IUPAC) has published a series of protocols on safety, efficacy, standardization, and documentation of herbal medicine in which aspects of phytochemistry and analytical chemistry feature, and in which strategies for quality control are discussed in detail (Mosihuzzaman and Choudhary, 2008). If fully implemented, these strategies from the World Health Organization (WHO) and IUPAC, will raise the scepter of traditional medicine from its rather jaundiced view in the eyes of most of "modern" medicine regulators and practitioners.

To understand that perspective, it is important to be aware of the goals for traditional medicine. One of the recognized goals is to be included as an integral aspect of a health system and for patients to be covered by health insurance for their use of traditional medicine products (and practices). That role in health care requires a strong evidence base, one which will assure safety and efficacy for both patients and practitioners founded on reproducible quality. *Phytochemistry is at the very core of that assurance*. So, with some notable exceptions, why isn't traditional medicine included as an integral aspect in most health systems now? Until certain myths associated with traditional medicines are dispelled, and a scientifically and technologically sound evidence base is developed, little progress towards acceptance will be achieved at the government policy and health professional levels.

Access to quality health care is a human right within Article 25 of the Universal Declaration of Human Rights of the United Nations (Anonymous, 1948). If traditional medicine is to fulfill its crucial role in global health, the long-standing, well-entrenched myths must be "busted" and solid pillars of science and technology erected to underpin the evidence base required for acceptability in the health system of a country. In recent articles (Cordell, 2007, 2008, 2009, in press-a), and more specifically in a book chapter (Cordell, in press-b), the author has begun to outline a selection of some new strategies which will contribute to enhancing the evidence base for traditional medicine. These strategies concern how national policies and regulations are formulated with respect to establishing standards for the quality of safe and effective traditional medicine products and practices; how research capacity on traditional medicine can be built; how the safe and effective use of traditional medicine can be promoted; and how there can be enhanced communication and cooperation within traditional medicine and with other medical practices. A selection of these strategies, all of which involve phytochemistry and the analysis of plant secondary metabolic profiles, as an integral aspect of their development, implementation, and application, includes:

- Develop policies, regulatory criteria, and technical guidelines which would provide and assure the continued availability of quality, safe, and effective traditional medicine products and practices based on the results of evidence-based research, and