JOURNAL OF HERBAL MEDICINE 5 (2015) 118–127

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hermed

Discussion

Phytochemical variation: How to resolve the quality controversies of herbal medicinal products?

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ARTICLE INFO

Article history:
Available online 8 May 2015

Keywords:
Medicinal plants
Herbal medicine
Herbal medicinal products
Phytochemical variation
Quality control
Chemical marker

ABSTRACT

Plants and plant products possess therapeutic potential and are duly utilized for the production of traditional as well as modern medicines worldwide. It is evident that the chemical composition of a plant and possible synergy of its constituents impart therapeutic potential to a plant or plant product(s) (HMPs). However, genomic composition, developmental stage and ambient environmental conditions often cause spatio-temporal variation in the chemical profile of plants. Likewise, harvesting techniques, post-harvest processing, storage conditions, widespread use of pesticides, frequent adulteration and microbial contamination also cause a notable variation in chemical profile of medicinal plant material. The occurrence of phytochemical variation in plant material obtained from different geo-biological sources eventually induce discrepancies in its therapeutic profile. Consequently a variation in chemical composition and therapeutic profile of plant material causes routine complications for the validation of therapeutic efficiency and safety of HMPs.

With the global upsurge in the usage of HMPs together with the concurrent reports on chemical variation, adulteration and safety concerns there is an urgent need to institute regulatory and diagnostic measures to meet the objectives of WHO Traditional Medicine Strategy 2014–2023. In this regard, DNA based diagnosis and quantitative profiling of chemical markers accompanied by conventional purity measurements should provide a complete set of quality assurance for medicinal plant material and HMPs. The implementation of an integrated approach of DNA barcoding and quantitative metabolomics has therefore become essential to ascertain potency, purity, consistency and safety of medicinal plants as well as HMPs practised in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine, Kampo and other systems of traditional medicines worldwide.

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http://dx.doi.org/10.1016/j.hermed.2015.04.002
2210-8033/

1. Introduction

Various archaic scripts of the Hindu, Chinese, Greek, Egyptian, Mesopotamian, Biblical and many other civilizations have documented the historical use of plants and other natural substances for medication since 5000 BC or even earlier (Chaudhary et al., 2001; de Pasquale, 1984; Dhami, 2013; Elfahmi et al., 2014; Gurib-Fakim, 2006; Touwaide and Appetiti, 2013). The retrieval of pollen grains of *Achillea*-type, *Althea*-type, *Centaurea solstitialis* L., *Ephedra altissima* Desf., *Muscari*-type and *Senecio*-type from 60,000 BC old burials of Shanidar IV gives the historical evidence of the ancient use of plants for medicinal purposes (Lietava, 1992; Solecki and Shanidar, 1975). In a contemporary context, the global estimate of flowering plants has amounted to nearly 350,000 species with the probability of a 10–20% increase (Joppa et al., 2011; Takhtajan, 2009; The Plant, 2013), of which about 30,000–85,000 species have been supposed to comprise medicinal properties, perhaps most of the known medicinal plants represent angiosperms and many are yet to be explored (Balunas and Kinghorn, 2005; Liu and Wang, 2008).

It is believed that biologically active chemical principle(s) and synergistic dynamics of all available chemical entities impart therapeutic potential to a plant or plant product(s) (Ulrich-Merzenich et al., 2009; Wagner, 2011; Yang et al., 2014). Large numbers of plant-derived pure chemical principles have shown vital therapeutic activities against various illnesses and many of them have eventually been assimilated into the modern pharmaceutical main-stream. In the modern pharmaceutical arsenal, nearly 50% of allopathic drugs and drug leads primarily came from natural resources whereas more than 25% of modern medicines, including the blockbuster drugs such as paclitaxel, vincristine, vinblastine and artemisinin, solely come from plant sources (Koehn and Carter, 2005; Mishra and Tiwari, 2011; Newman and Cragg, 2012). In contrast to the allopathic formulations that contain defined amounts of therapeutically active chemical principle(s), Herbal Medicinal Products (HMPs) usually comprise a defined amount of plant material but seldom mention the concentration of bioactive principles therein. Similarly, variation of bioactive metabolites in plant material obtained from a different geographical origin eventually incurs great difficulties in determination of potency, purity, consistency and safety of medicinal plants and HMPs (Brown et al., 2003; Sidhu et al., 2011). This review primarily focuses on highlighting the risks prompted by the phytochemical variation of medicinal plants and HMPs as shown by contemporary studies, followed by suggestions for regulatory amendments and diagnostic strategies to ensure safe and effective use of HMPs.

2. Phytochemical variation is a common phenomenon in medicinal plants

The presence of apparently low and variable amounts of bioactive metabolites in different parts of the plant and the use of plants from different geographical origins are the major limiting factors to the determination of their therapeutic quality assessment that eventually causes challenges for quality assurance of HMPs. The qualitative variation that genetic composition and the developmental stage of a plant along with the prevailing environmental perturbations primarily determine the metabolite profile of plants, especially the nature of metabolites and their concentration in a particular plant tissue. Quantitative variation of a particular compound usually varies in the plant material from different locations. As a consequence, different populations of medicinal plants that have originated from various geographical sources and harvested in different seasons exhibit distinct spatio-temporal variation in their phytochemical profile (Binns et al., 2002a; Hussain et al., 2008; Lubbe et al., 2013; Siriwardane et al., 2013). Harvesting, processing and storage-related alterations also impart notable changes in the chemical profile of any plant material (Booker et al., 2014; Griggs et al., 2001; Laher et al., 2013). Similarly, microbial contaminations and insect infestations also induce marked variation in the chemical profile of herbs and herbal products (Kneifel et al., 2002; Romagnoli et al., 2007; Tassaneeyakul et al., 2004). In addition, uncontrolled use of pesticides and systemic accumulation of toxic pollutants in cultivated medicinal plants inevitably impose critical risks to assuring the quality of herbal products (Cheng et al., 2013; Dogheim et al, 2004; Kosalec et al., 2009; Sarkhail et al., 2012; Zuin and Vilegas, 2000). Systemic and deliberate adulteration with foreign plant material and mixing of old or otherwise exhausted plant material along with the use of other foreign material further intensify the risks of blending unrelated and, in many cases, seriously hazardous chemical entities in herbal products (Foster, 2011). There is evidence of the adulteration of bilberry products with potentially hazardous and banned synthetic dye materials as well as charcoal and low cost anthocyanin containing fruits (Foster and Blumenthal, 2012) and adulteration of root, rhizome and preparations of Black Cohosh (*Actaea racemosa* L.) (Foster, 2013) which illustrates the severity of intentional and fraudulent adulteration of herbal products. Furthermore, phytochemical analysis of plant material obtained from different geographical sources and their herbal products shows remarkable variation in the type and concentration of different phytochemicals therein.

For instance, the rhizome of *Curcuma longa* L., a common herb belonging to Zingiberaceae family that possesses an indeterminate history of medicinal and cosmetic uses in Ayurveda and Traditional Chinese Medicine, has displayed a notable variation in curcuminoid content and essential oil composition from different geographical origins (Pothitirat and Gritsanapan, 2006; Singh et al., 2010; Sumathi et al., 2008; Tønnesen et al., 1989). Different commercially available turmeric varieties as well as marketed turmeric curry powder have shown a curcumin content of 1.06–5.65% which is one of the most promising bioactive curcuminoids (Jayaprakasha et al., 2002; Tayyem et al., 2006). Whereas Pothitirat and Gritsanapan (2006) reported 7.0–8.20% (v/w) of essential oil and 3.07–9.58% (w/w) curcuminoids in the turmeric samples obtained from different locations of Thailand.

Similarly, *Ocimum basilicum* L. and other *Ocimum* L. species of the Lamiaceae family that are common Ayurvedic herbs have shown a distinct variation in the concentration of terpenoids, especially linalool, estragole, limonene, camphor, epi-α-cadinol and α-cadinene (Chalchat and Ozcan, 2008; Grayer et al., 1996; Klimánková et al., 2008). Phytochemical