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Review

Integrated analytical assets aid botanical authenticity and adulteration management

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ABSTRACT

This article reviews and develops a perspective for the meaning of authenticity in the context of quality assessment of botanical materials and the challenges associated with discerning adulterations vs. contaminations vs. impurities. Authentic botanicals are by definition non-adulterated, a mutually exclusive relationship that is confirmed through the application of a multilayered set of analytical methods designed to validate the (chemo) taxonomic identity of a botanical and certify that it is devoid of any adulteration. In practice, the ever-increasing sophistication in the process of intentional adulteration, as well as the growing number of botanicals entering the market, altogether necessitate a constant adaptation and reinforcement of authentication methods with new approaches, especially new technologies. This article summarizes the set of analytical methods - classical and contemporary – that can be employed in the authentication of botanicals. Particular emphasis is placed on the application of untargeted metabolomics and chemometrics. An NMR-based untargeted metabolomic model is proposed as a rapid, systematic, and complementary screening for the discrimination of authentic vs. potentially adulterated botanicals. Such analytical model can help advance the evaluation of botanical integrity in natural product research.

1. Introduction

Botanicals (here defined as plants or parts of plants, but also lichens, fungi, and algae) used for medicinal purposes or health maintenance can be sold as plant raw materials or included in various preparations categorized as (traditional) herbal medicines or herbal products [1–4], herbal/botanical drugs [5], phytomedicines, natural health products [6,7], dietary supplements (DSs) [8], or food supplements [9], according to their final intended uses, and in compliance with prevailing regulatory requirements. The term botanical(s) is utilized here in lieu of plant raw material(s), or herbal raw material(s). Considering that botanicals are the building block of any commercialized finished products, determination of their authenticity is fundamental to supporting the purported effects and/or efficacy claims, as well as assuring the overall safety of any finished/commercialized product.

Regardless of their legal status, botanicals and their preparations play an important role in worldwide health care systems, and in many parts of the world they remain integral components of primary health care. In developed countries, herbal medicines/botanical DSs are increasingly utilized in complement with - as a first line of treatment for common ailments before considering the use of pharmaceutical drugs, or to address specific health concerns - or as alternatives to prevailing medical paradigms. The widespread consumption of botanicals, especially in the developed world, has significant economic impact, with the botanical DS market in the U.S. alone representing approximately $7 billion for the year 2016 [10].

Quality assurance of botanicals is regulated primarily at the national level as a function of their legal status e.g., herbal drugs, traditional medicines, or food supplements [11,12,14]. This means that, in essence, the globalized botanical supply chain is not supported by a harmonized framework for the evaluation of botanical quality and authenticity. Incongruent statutory frameworks and the variety (and meaning) of quality control (QC) terminologies contribute to a certain level of confusion among consumers and international stakeholders alike [6,8]. This lack of a general agreement as to (a) the meaning of botanical authenticity and (b) the technical requirements related to certification of botanical quality increases the threat of botanical adulteration [15].

In academic research, the reproducibility and consistency of preclinical outcomes dedicated to evaluating the efficacy and safety of botanicals can be affected by use of insufficiently characterized

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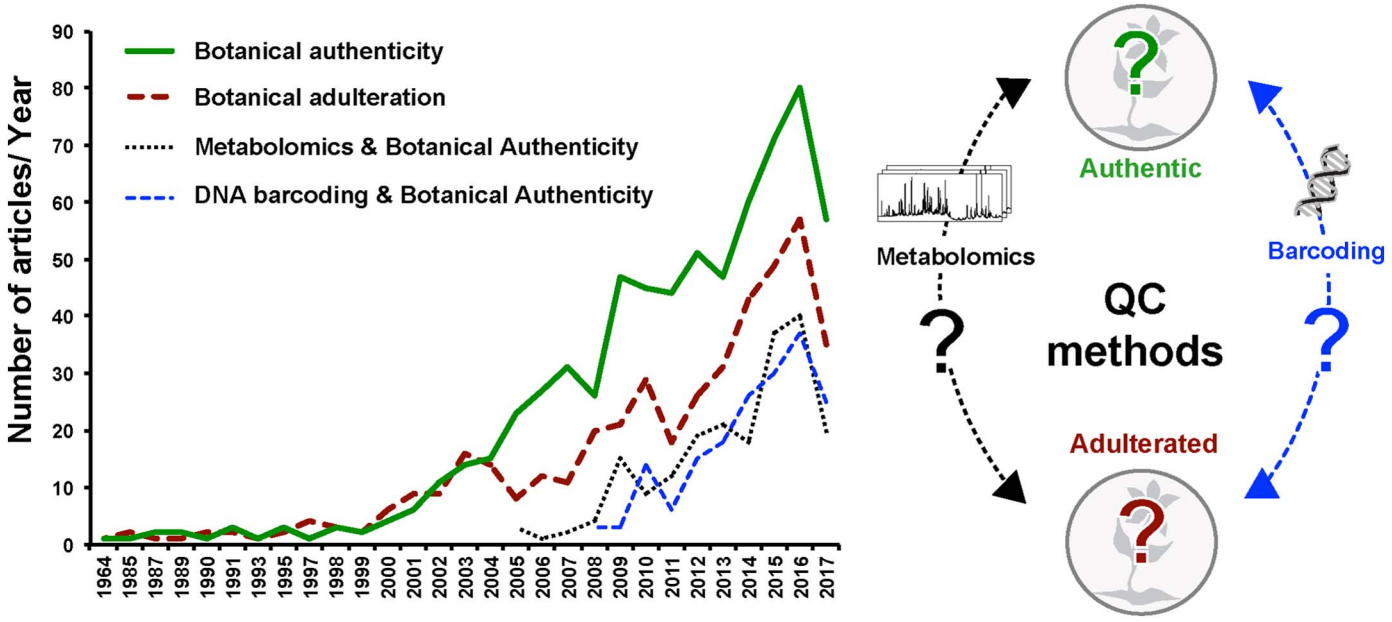

Fig. 1. Publication trends extracted from PubMed (status: October 2017) and related to the following themes: botanical authenticity, botanical adulteration, metabolomics, and DNA barcoding techniques in relation to the concept of botanical authenticity. The extracted publication counts highlight the strong interconnections between the notion of botanical adulteration and authenticity and the new/modern approaches for the assessment of botanical authenticity. This article proposes to evaluate the relationship between botanical adulteration and authenticity, while assessing the role of DNA barcoding and metabolomics/chemometrics in the QC process to discriminate authentic and adulterated botanicals.

material, for both crude samples and extracts, for which authenticity has not been assessed carefully [16]. In order to address this problem, the U.S. National Institutes of Health (NIH), via its National Center for Complementary and Integrative Health (NCCIH; formerly NCCAM) has developed policies (NOT-AT-05-003/004), which have been applied to NIH-funded biomedical research involving natural products since 2005. These have evolved into the current NIH Product Integrity Policy (PIP), which is available for consultation online at (https://nccih.nih.gov/research/policies/naturalproduct.htm). PIP stipulates that the identity and quality of botanicals, purified compounds, and other natural products utilized in NIH-funded research must be clearly established [17].

Reflecting increased public demand and scientific awareness, the number of studies dedicated to the authentication of botanicals and detection of adulterations has increased considerably in the past decade (Fig. 1). This observation parallels the popularization of techniques such as DNA barcoding, phytochemical profiling/fingerprinting, metabolomics and chemometrics being applied to botanical authentication processes. Regardless of the techniques employed, according to our literature survey both concepts of botanical authenticity and adulteration have shown interdependency.

The main objective of the present study is to propose a clarification of the integrated notion of botanical authenticity vs. adulteration, while emphasizing the relevance of a multilayered analytical strategy combining classical and contemporary techniques for the assessment of botanical authenticity. This article will not address problems relative to authentication of finished products, although many of the reviewed analytical methods will be applicable to them. Three key questions will be discussed herein: (1) what is/are the meaning(s) of botanical authenticity, and how does it relate to the problem of adulteration? (2) What is the contribution of targeted and untargeted analysis to the determination of both authenticity and adulteration? (3) What is the place of metabolomics in the QC toolset for the assessment of authenticity? In line with the third question, an untargeted metabolomic model will be proposed for the systematic screening of botanical samples. Ultimately, this article advocates for the dissemination and implementation of modern analytical tools/concepts that together can better address the determination of botanical authenticity with the stepwise discrimination of potential adulteration.

2. Exploring the meaning of authenticity and its relation to adulteration

2.1. The different facets of botanical authenticity

Terms are words or expressions that, in a specific context, are given specific meanings. Accurate and unambiguous terminology is fundamental to defining the concepts, terms and methodologies, collectively utilized in the inter-disciplinary activities conducted as part of botanical authentication. According to our literature survey, there is no official or unified definition of botanical authenticity, and, thus, a proposed definition of what makes a botanical "authentic" is somehow needed.

Authenticity involves (www.merriam-webster.com) "*being exactly as claimed, certified and certifiable, conforming to an original*", with related words being "*validated, verifiable, correct, pure, unadulterated*". In order to be conforming to an original, a botanical material should be identical, or share as many identical features as possible with that original.

The notion of identity is, therefore, inherently part of authenticity (Fig. 2). Botanical identity relies on a genetic or phenotypic delimitation, identification of the part(s) of the plant used, and/or an analysis of the characteristic chemical composition of a botanical, made under specified extraction conditions, that appropriately reflects its metabolomic profile at the time of harvest [4,18,19]. The phytochemical composition of genetically identical plant material can be affected by the composition of the soil, cultivation conditions, time of harvest, drying and extraction processes performed on the plant materials (Fig. 2). These parameters, with the exception of extraction, illustrate the concept of traceability.

Definition of authenticity, when applied to products such as food plants or processed foodstuffs, encompasses the certification of origin or supply chain transparency as well as the validation of composition in agreement with a certain mode of preparation. In the European Union (E.U.), the certification of origin contributes to the authenticity and economic value of food products, and, most importantly, ensures consumer safety [20,21]. Consequently, traceability is a primary contributor to authenticity.

The concepts "*pure, unadulterated*" stand in close relation to