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Mini Review

Open Space Knowledge and Data and Their Influence on Natural Products Based Self-Medication Trends

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Introduction

Contemporary academic (conventional) medicine, based on current advancements in life sciences and applying evidence based efficacy and safety principles, has evolved from ancient cultures of well-being and healing practices, which originated in prehistoric times, and it co-exists with their ethno-medicine remnants conveniently described as complementary and alternative medicine (CAM) [1, 2]. Global healthcare crisis, which has led to acceptance and even encouragement of CAM practices as an aid to conventional medicine, is a phenomenon of great complexity, comprising processes of various speed and dynamics. In this mini-review we'll limit discussion to influence of IT and novel scientific knowledge dissemination systems, such as Open Science, to self-medication applied with legally available biologically active substances, but not limited to the OTC drugs.

Discussion

The 21st century societies differ dramatically from an earlier populations in respect to availability of sound scientific knowledge and specific technical information in every field imaginable, due to widespread IT access (www) to primary source scientific publications and reasonable coverage of scientific achievements through the media. Considerable rise in general education level and computer literacy allowed for massive, profiled individual internet searches, and using their results for informed choice of medicinal and/or CAM treatments. Consequently, a new type of medical patients and pharmacy customers have been created, with considerable potential of modifying future trends on medicinal product markets. Inefficiency of state healthcare systems became notorious not only in the "poor South" regions, but also in the most affluent societies of the industrialized West. In the first case, even relatively small number of WHO selected essential drugs are scarcely available; in the second – thousands of innovative, proprietary active pharmaceutical ingredients (API of the ethical or brand drugs), supplemented by experimental therapies with new molecules in advanced clinical trials, are extremely expensive, with their costs only fractionally covered by insurance. Moreover, efficacy of modern medicines in general is far from satisfactory. This is well exemplified by mortality and morbidity statistics from such principal non-transmittable disease killers as cardiovascular disorders, tumors, and metabolic syndrome, including diabetes [3]. It should be reminded that API substances, estimated as a collection of a few thousand molecules of low molecular weight (biological drugs like vaccines or antibody conjugates form much smaller assembly), consist of a very small fraction of known molecules (ca. 10^8 chemical entities recorded by CAS database), while natural product collection (e.g.: alkaloids, antibiotics, flavonoids, glycosides, isoprenoids, phenolics, vitamins, etc.) is estimated at 200 thousand, with a fair chance of further growth with advancement on microbial, plants and aquatic organisms metabolome studies. It is therefore not surprising that natural products and especially secondary metabolites (SM), which were developed and genetically encoded as evolutionary traits which provide hosts with some marginal environmental advantages, formed at first a solid base for ethnopharmacology and specifically herbal medicine, and in more recent times afforded countless leads for modern drugs [4,5]. Particularly, among drugs applied in oncology, SM-derived substances account for approximately 60 % of APIs (well-known examples include: taxanes, dimeric indole alkaloids from *Catharantus* (former *Vinca),* anthracyclines, camptothecins, podophylotoxins, etc.). These compounds feature selective toxicities, but in general they are biocompatible and follow predictable metabolic pathways, in contrast to many synthetic compounds obtained by combinatorial synthesis for high-throughput screening. Pharmacognosy, a science of SM medical application, which started at the beginning of 19th century with discovery of alkaloids, was for a long time very close to herbal medicine, which concerned itself mainly with whole plants extracts and concoctions, while individual chemical entities pharmacology development was considerably limited by progress in chemical separation techniques and advancement in analytical chemistry. Currently, legal access to biologically active compounds for nonprofessionals is widely differentiated: from ban on tightly controlled markets of the prescription drugs, through regulations concerning registered over the counter medicines (OTC), to herbal medicines and materials, including high chemical purity isolates of SM, for which various local regulations may apply. The last category is particularly interesting from the point of view of CAM and self-medication, in view of general availability. The herbal medicine markets are already well developed and characterized by dynamic growth. In the US alone, the value of herbal medicines market topped 8 billion $ in 2017, with over 12% growth from year 2016, while the global market value is currently estimated at ca. 100 bln $

[6]. Herbal materials can be segmented into: herbal pharmaceuticals (phytopharmaceuticals; the dominant category), herbal functional foods, herbal dietary supplements and herbal cosmetic products. From the formulation point of view, extracts accounts for the largest markets, and are likely to retain the leading position for a while. In terms of the botanical classification, products derived from the following plants are considered the most significant*: Marrubium vulgare, Cinnamomum spp., Vaccinium macrocarpon, Echinacea, Camellia sinensis, Curcuma longa, Actaea racemosa, Aloe vera, Zingiber officinale, Cocos nucifera, Silybum marianum, Gingko biloba, Malpighia punicifolia.* Hospital and retail pharmacies are the main distribution channels thus far (over 55% market share) but the internet (e-commerce) sector already shows great potential.

The leader of the herbal products market value classification is, by a large margin – curcumin (turmeric), which is unique in many respects and therefore deserves few comments. The main phenolic constituent of *Curcuma longa* rhizome (traditional Indian spice and medicine deeply rooted in Ayurveda system and used throughout Asia under various names) was identified as diferuloylmethane at the beginning of 20th century, and its synthesis was completed thereafter to study a new type of plant pigments capable of dyeing cellulose fibers directly [7]. Turmeric powder, a spice and pigment known as a constituent of food additive popularized in the West as curry, which contain some closely related curcuminoids, is produced in India in multi-ton quantities and distributed by major producers of herbal medicines (encoded E 100 as a food additive and granted the GRAS status by Joint FAO/WHO Expert Committee on Food Additives). High chemical purity curcumin, which became a very popular biochemical and pharmacological molecular probe after initial pharmacological screening, is also freely available. First recognized as an efficient antioxidant, inhibiting COX, LOX and cytochrome P450 promoted metabolism of arachidonic acid, soon attracted attention as an agent which performed extremely well in antiproliferative and antitumor tests [8, 9].

An extensive discussion of curcumin molecular targets, which include transcription factors, growth factors, protein kinases, apoptosis-related proteins, etc., based on the compound structure and chemical reactivity was expertly summarized by concluding that nearly all human cell lines can be inhibited by the compound *in vitro*; however a big gap exists between its unquestionable pharmacodynamics potential and its feeble pharmacokinetic efficiency, which results from poor solubility, limited metabolic stability and rapid biotransformation in biological media [10]. Such conclusions are in keeping with results of numerous clinical trials, recorded by NIH and reported on PubMed. Meanwhile, search for "curcumin" on Google Scholar (July, 2019) returns ca. 375 000 hits in a small fraction of a second, reflecting a hype of great expectations generated by an avalanche of investigations which suggest medicinal applications of the compound, in particular for prevention and treatment of cancer related ailments. This, obviously is not without influence on a hypothetical well informed customer, interested in a self-care continuum activities, which consists not only of self-managed ailments in minor cases, but includes lifestyle choices (e.g. diet and its supplementation) aimed at long term disease prevention, or intervention in an acute condition. Curcumin seems to provide a good example to illustrate thesis, that an interest in natural products (SM), supplied in form of high purity chemical entities, may soon transform herbal material markets beyond recognition, since all technical means are in place to satisfy such demands. In particular, for many SM with less complicated structures, synthetic chemistry alternatives to isolation exists; next, biotechnology is in line, with growing assembly of gene sequences and clusters which can be expressed in microorganisms already validated for industrial use. In case of a therapeutic indication applications, various sources of the active ingredient may evoke some formal controversies, calling for high-tech arguments based on sophisticated analytical technologies [11] but for "established use" natural products marketing authorizations are usually more freely available. "Adulteration" of natural products with the same substances of synthetic origin are likely to be treated case by case since precedences exist: e. g. some of the curcumin clinical trials were carried out with use of synthetic origin substance.

While the curcumin story stands out among other herbal medicines likely to be applied in CAM procedures, in terms of great abundance of pharmacological results already amassed, it certainly is not the only one plagued with problems of low bioavailability which results in lack of *in vivo* efficacy. To this point, some facts from the rich history of ascorbic acid (Vit. C) medical applications should be reminded. Recognition of antiscorbutic action of Vit. C isolated from citrus fruits, was followed by Albert Szent-Győrgyi observation that it worked much better in the presence of green pepper flavonoids, temporarily advanced to a vitamin status [12]. The value of ascorbic acid for fighting cancers is disputable and necessity for exorbitantly large doses delivered by intravenous injections is discouraging [13], but the idea of "enhancers", which are not active *per se* but significantly improve bioavailability of other API substances is alive and well. For curcumin, alkaloid piperine is indicated as the effective enhancer, and co-formulations of these compounds are believed to secure progress towards improved BA. Flavonoids, which are a large family of SM, closely related by phenylpropanoid biogenetic pathways, have not recovered vitamin P status, but many compounds from that category feature extremely interesting biological activities with prospective medicinal applications: in practically all structural sub-categories – chalcones, flavanones, flavonols, flavones, isoflavones, catechins and anthocyanes there are numerous examples of such health promoting activities, which are attractive from the point of view of CAM practices and metabolic syndrome prevention [14].

Genistein, the isoflavone with the most publicized record of research in oncological pharmacology [15, 16] should in principle be available in multi-ton quantities, since one of the main agricultural crops in global scale – the soybeans (over 300 mln tons harvested annually) contain on average ca. 0.1% of the compound, but thus far has not made it to natural origin chemicals distribution channels at affordable prices. Despite of its poor oral bioavailability, interest in genistein chemopreventive potential is high, GRAS status secures entry into modified food segment, and the compound is relatively easily available from chemical synthesis. Like in the case of "Indian gold" – curcumin, there is no shortage of sound, scientific information on flavonoids pharmacological activity, propagated through Open

Access channels. In summary, a number of individual chemical entities of natural origin ready to join traditional pool of herbal medicines is large, which offers an outstanding opportunity for healthcare related innovations, focused on opening markets for new type of customers seeking specified, high quality materials from SM category, for self-managed healthcare.

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