ONOMY Science

American Journal of Toxicology & Research
ISSN 2688-3155

Research Article Open Access

Plant Phenolics in Complementary and Alternative Medicine and In Self-Medication

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Citation: Plant Phenolics in Complementary and Alternative Medicine and In Self-Medication: Am J Toxi & Res. 2019; 1(2): 001-005.

Submitted: 26 August 2019; **Approved:** 30 August 2019; **Published:** 31 August 2019

Abstract

In this short commentary, chemical point of view on possible physiological, pharmacological and toxicological effects of polyphenolic xenobiotics of natural origin is presented, particularly in reference to their consumption with diet, functional food and dietary supplements. Since proportion of natural phenolics among plant secondary metabolites which are ingested with fruits, seeds, nuts, herbs, spices, and vegetables (highly recommended for human well – being) is high, the question of possible toxic effects of these compounds, their possible contaminants, and adulterations, should not be ignored. Few examples, with some focus on ubiquitous flavonoids, are discussed in certain detail, in order to expose complexity of interactions between phenolic chemicals and biological networks such as mammal organisms. In view of strong tendency towards self-medication with help of complementary and alternative medicine (CAM) means, which are now widely available through retails and e-commerce, caution should be advised, particularly when multicomponent preparations with inadequately specified content and chemical purity are taken into account.

Keywords: Secondary Metabolites; Plant Phenolics, Polyphenols; Flavonoids; Phytopharmacology; Pharmacognosy; Phenol Reactivity; Natural Products Structure Elucidation And Quantification, Metabolism; Toxicity; Metabolomics; Metabonomics; Herbal Medicines; Dietary Supplements

Introduction

Healthcare is of primary concern for individuals, as well as for every social organization imaginable, and pharmacological interventions with a prescription drug (or equivalent preparation) application are considered as an imminent part of a post-diagnosis treatment. For most of global population medications acquired from natural sources must suffice, because of unavailability and unaffordability of modern western medicines designed and developed in industrialized countries [1-4]. Paradoxically, affluent societies are also plagued with a multitude of health problems among which epidemic increase in metabolic syndrome (including diabetes and cardiovascular ailments), cancer, and neurodegeneration are not less deadly than much feared communicable and parasitic diseases. Generally unsatisfactory performance of pharmaceutical industry in fulfillment of efficacious and affordable drug delivery mission, has resulted in translation of traditional ethnopharmacology and academic pharmacognosy into new search tools for extending natural products exploited thus far in the CAM niche into more general quest for individualized self-healthcare management with use of plant materials [5,6]. Traditional pharmacognosy identified plethora of plant natural products (secondary metabolites; SM) for which now sound scientific data exist, supporting deeply rooted hypothesis concerning their beneficial human health effects. In popular belief medicinal products are safe when used according to prescription and the same applies to wide selection of "natural" medicines. Since in fact there is a basic difference in safety level between clinically validated registered drugs and rather poorly specified herbal materials, some discussion of advances in evaluation of main categories of natural products chemical analysis and pharmacologi-

cal/toxicological testing seems timely.

Plant Phenolics as Biologically Active Constituents of Diet and Dietary Supplements

Due to advancements in life sciences and readily available medical information (www), large number of people undertake various individual activities involving some diet modification or supplementation, aimed at health preservation or therapeutic intervention, outside of official healthcare systems, which are often judged insufficiently available and non-efficient [5]. In the western world, there is plenty of room for such activities since apart from tightly regulated prescription pharmaceutical preparations dispensed by retail pharmacies, large poorly controlled markets exist for "natural remedies" like herbal drugs, phytochemicals, dietary supplements, functional foods, and even individual active ingredients of plant origin [7-9]. Natural products have served as the principal inspiration for drug discovery efforts since 19th century, when isolation of distinctly biologically active plant alkaloids coincided with birth of synthetic organic chemistry and dawn of the era of man-made pharmaceuticals. Current estimates reporting over 250 thousand species of flowering plants to occur globally, concomitantly indicate that relatively low fraction of the resources have been thoroughly explored thus far. Nevertheless, majority of contemporary drugs in many therapeutic areas (e.g. anticancer, antibacterial, antiviral) are derived directly or through some minor synthetic modifications from natural sources [4,9]. Secondary metabolites (SM) of various biogenetic origin, which contain hydroxylated aromatic (phenolic) components in their structure, comprise the largest proportion of total collection of natural products, presently estimated at 200 thousand chemical individuals of low molecular weight. These compounds are most often referred to as polyphenols or polyphenolics, which suggests multiple hydroxylation of the aromatic rings. This classification stems from tradition of the plant constituents investigation, aimed primarily at technical applications like animal skin tanning into leather, natural dyes, and connected technologies of the past [10-12]. For the purpose of this short review we prefer to apply for such SM less restrictive term of plant phenolics, which include not only monohydroxylated aromatics but also their derivatives such as glycosylated or alkylated phenolic compounds. The main categories of plant phenolics, ubiquitous in edible plants are: hydroxybenzoic acids; flavonoids (flavones, flavanols, flavonols, isoflavones, aurones, anthocyanidins, procyanidins); stilbenes; lignans; coumarins [13-15]. All that compounds feature chemical functionality rendering them strong antioxidative properties, believed to play supportive role for intrinsic cellular mechanisms responsible for scavenging aggressive reactive oxygen species, which can threaten integrity of biomacromolecules and biological membranes [7,11,16]. Naturally, apart from generic properties such as antioxidative action (which is often associated with anti-inflammatory activity) individual plant phenolics feature complex and pleiotropic network pharmacology [17-19], further complicated by diverse pharmacokinetics and metabolism of the host and its microbiome [20]. In traditional pharmacognosy and also throughout 20th century, herbal materials allowed in medicine on basis of well documented "established use" were often specified by use of modern analytical techniques, but determination of one selected marker – a low molecular chemical compound of known structure and biological activity, was considered sufficient from the point of view of quality assurance and patients safety. We have inherited from pedecessors vast knowledge on how certain plant concoctions can help curing common human ailments. Excerpt from a large collection of commonly used plants, popular in the West and gradually absorbing from Ayurvedic and Traditional Chinese Medicine sources, include among others: Curcuma longa L. (turmeric); Echinacea purpurea L. (echinacea); Ginkgo biloba L. (ginkgo); Hypericum perforatum L. (St John's wort); Panax ginseng L.A. Mey. (panax); Valeriana officinalis L. (valeriana); Matricaria chamomilla L. (chamomile); Allium sativum L. (garlic); Trigonella foenum-graecum L. (fenugreek); Sylibum marianum gaertn. (milk thistle); Tanacetum parthenium Schultz-Bip. (fewerfev); Zingiber officinalis Roscoe. (ginger). Owing to the extensive research efforts in academic phytochemistry, structural identification of one of more active ingredients of the healing plants were achieved during 20th century, advancing herbal materials to the level of standardized medicines. Gradually, it became evident that certain types of biogenetic pathways are more widespread in the plant kingdom, resulting in common occurrence of such compounds like phenolics (an their sub-class, flavonoids), which apparently can play multiple roles in plant physiology and also in their environmental interactions. Remarkable advances in complex and sophisticated analytical techniques now can assure separation, structure elucidation and quantification of multicomponent mixture, even below nanomolar level, in a single experiment. As a result in a revolutionary change in potential of combined analytical technologies like HPLC/MS/MS ; GC/MS ; CE/MS and HPLC/NMR, multinuclear NMR and accelerator MS, a single compound monitoring became completely obsolete. The current standard of phytochemical analysis, which developed in great part as a translation of proteom-

ic studies, has gone through a transient phase of chemical fingerprinting, which strive for identification of as many natural compounds in a biological material sample as possible and arrived at metabolomics (elucidation of entire collection of low molecular weight compounds of primary and secondary metabolism) and metabonomics (indicating qualitative and quantitative changes in metabolome under influence of disease, pathogens, therapeutic intervention, diet, life style, etc.) [21-23]. Naturally, such radical change in a way of system biology description, in terms of array of biochemical molecules composition and their content dynamics, requires processing a large amount of data and specific logistics supported by IT, for their handling. It will suffice to mention here that human metabolome itself may contain as many as 150 thousand of small molecules, and its interactions with "foreign" metabolomes of edible plants and human microbiota, inevitably creates a network of biochemical interactions of paramount complication. Functional analysis of such metabonomic situation must be extremely difficult, considering a number of variables to be accounted for, which come from changes in: genetics (e.g. SNP – single nucleotide polymorphism), microbiome, epigenetics, and level of exposure to environmental chemicals. [24]. It is not surprising that postulates like necessary prevention, and need for personalized medicine and precision nutrition, now replace old fashion ideas and practices based on simplified notion of the ailment – treatment relationship [5,25,32]. Such calls are not without response from general public, which is anxious to cope with increasingly evident threat from so called civilization diseases, comprising metabolic syndrome with cardiovascular diseases, cancer and neurodegeneration, not to mention possible epidemic of communicable diseases. Throughout the changes from ethnopharmacology to metabolomics based systems biology, plant phenolics have managed to retain an opinion of multi-target biologically active compounds which feature a variety of selective toxicities with prospective utility as drug leads for treatment of cancers, parasitic diseases, bacterial and viral infections, etc. [3,11,26,27]. Their general, supposedly beneficial anti-oxidant activities may not be sufficient reason for uncontrolled distribution and use; despite of the facts that increasing number of individual plant phenolics already have sound pharmacological monographs, caution and calculated risk analysis should be advised, especially when poorly specified plant tissues, extracts and concentrates are considered. It should be mentioned that even for renown manufacturers of dietary supplements, independent expert analyses revealed considerable differences between label composition and real content of the active ingredients [28]. Raw plant materials can be unintentionally contaminated with bacteria or other biologics, as well as with heavy metals or soil constituents [29]. It can also be purposely adulterated either with foreign matter or with organic substances of synthetic origin, sometime mimicking activity of the plant active constituents [30]. All such cases can be relatively easily revealed, but not without engagement of highly trained analytical staff equipped with sophisticated instrumentation, like thermo-cyclers for identification of foreign DNA via polymerase chain reaction amplification (PCR), inductively coupled plasma sector field mass spectrometry (ICP-SFMS) for heavy metal analysis, and high performance liquid chromatography with quadrupole mass spectrometric detector (HPLC/MS/MS) for other environmental contaminants and synthetic chemicals determination. [29,31] Since plants can contain several hundreds of SM, multi-herbal compositions and multicomponent dietary supplements are particularly difficult to assess from the point of view of individual patient safety. While principal active constituents are expected to follow rules of classical pharmacology/toxicology, advanced pharmaceutical and clinical analyses find some cases of hormetic biological activity at very low concentrations, from compounds which were not even identified in a given plant, before thorough metabolomics examination. Therefore, it can be concluded that individual compounds, known as secondary metabolites, isolated from identifiable natural sources and available in a state of well specified, high chemical purity, deserve better recommendation as a personal choice for dietary supplement or even self-medication. The notion of unmet medical needs, which drives pharmaceutical industry R&D, can now be translated to wider perspective of societies and populations with unsatisfactory access to modern drugs and contemporary medical technologies. Unlike registered prescription drug markets, which are highly restrictive and very slow in response to newly defined patients' needs, markets of complementary and alternative medicine products, herbal medicines, dietary supplements and functional food are very flexible and quick in satisfying popular demands. Remarkably, as a relatively new feature, an offer of single SMs, as an active ingredients, specified and labeled with defined chemical purity, has formed a dynamically growing fraction of the market. Products like: apigenin, astaxanthin, berberin, betulin, baicalin, catechins, curcumin, ellagic acid, genistein, kaempferol, koenzyme Q10, lutein, puerarin, resveratrol, rutin, quercetin, silimarin, and many others, are now commercially available even for an individual customer, from multiple manufacturers.

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Conclusions

Animal metabolomes co-evolved within environment rich in plants, which produce a great structural variety of secondary metabolites (SM) among which chemically reactive phenolic compounds, likely to perform variety of allopathic functions, predominate. Herbivores learned to avoid systemic poisons of plant origin, and to take advantage of selectively toxic SMs as adaptogenes, modulators of metabolism, and inhibitors of stressful processes that challenge homeostasis. The idea that vegetable food contains non-nutrients which are essential for health preservation became generally accepted [6,7,32]. Current holistic approach to human physiology and healthcare, complies with epigenetics, which treats exposition to xenobiotics as an interaction between biologically active compounds and biological systems, without differentiating impacts exerted by dietary foods, pharmaceutical drugs and environmental poisons. Previously distinctly different fields of study like physiology, phytochemistry, pharmacology and nutrition, presently tend to amalgamate under umbrella name of systems biology. That change was fostered by radical progress in basic science (e.g. genomics and the following "-omics"), paralleled by unprecedented advances in analytical technologies, which made metabonomic studies possible. Remarkably, current accumulation of new knowledge in life sciences area is, by a large part available in the public domain, through an open science media. This inevitably results in rise of a new type of customer, making his own literature research before deciding what products from expanding markets of OTC drugs, herbal products, dietary supplements and functional foods should be selected to satisfy individual needs. It is very likely, that such well-informed customers will seek products with sound specification and validated quality and safety, which in turn may favor producers of pure active ingredients over multicomponent compositions. Although in the past isolation of pure SM was considered difficult and inefficient, contemporary separation techniques largely reduced the burden of technical scale isolation of valuable plant constituents. Moreover, new biotechnological and synthetic methodologies are already in place to supply even structurally complicated SM like complex phenolics, flavonoids, etc., in a state of high chemical purity, which helps their evaluation as safe, health promoting natural products.

Conflict of Interests

The author declares no conflict of interest concerning this publication.

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