

Medicinal and Aromatic Plant Research in the 21st Century

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Abstract

It has been estimated that 250,000 terrestrial plants contribute to biodiversity on earth. The chemodiversity of plants, however, may be considered to be much larger due to the vast number of phytochemical constituents with their wide range of bioactivity as seen in medicinal and aromatic plants. The present review focuses on the potential of medicinal and aromatic plants for medicinal, nutritional and other purposes, but highlights also possible toxicities. Quality control for standardization of herbal products as well as advancements in molecular biological techniques will foster the progress of medicinal and aromatic plant research in the years to come.

Keywords: Food science; Natural products; Pharmacognosy; Quality control; Synergistic interactions; Toxicity

Introduction

The use of medicinal plants is as old the history of manhood. Archaeological sites show plants for healing purposes as for example the Lascaux caves in France, which are between 15,000 and 27,000 years old [1]. Even more, the history of herbal medicine seems to have its very first roots in the animal kingdom. Fascinating evidence exists for self-medication among non-human primates. Chimpanzees, bonobos and gorillas swallow specific leaves and chew bitter piths, if they suffer from parasite infections. It has been speculated that ancient shamans and healers learned from apes by observing them while they were taking medicinal plants. These plants were then taken by local human populations for medical purposes [2]. The ancient knowledge on the beneficial activity of some plants was a privilege of shamans and healers and give reason to establish traditional medicines worldwide. While many forms of traditional medicines were handed down orally from generation to generation for millennia [3-5], complex forms with written textbooks and education systems also developed, e.g. in traditional Chinese medicine, Japanese Kampo medicine, or Ayurveda [6-8].

Secondary metabolites of medicinal plants

The chemical constituents of plants can be categorized into primary and secondary metabolites. Primary metabolites serve nutritional purposes, e.g. sugars, fats, proteins. Secondary metabolites are not essential for direct survival of cells or organisms. They are required by plants as weapons against competitors, herbivores, or pathogens. It may sound trivial, but plants are immobile and this circumstance is a considerable evolutionary disadvantage, since they cannot escape herbivorous attacks by running away. As a self-defense strategy, plants started to develop biosynthesis pathways for noxious compounds during evolution of life to discourage predators. Secondary chemical compounds also take over the role of the immune system of animals. They may serve as bio-pesticides towards pro- and eukaryotes. Therefore, it comes as no surprise that plants represent a valuable reservoir to identify and develop novel natural and bio-degradable pesticides [9]. However, the spectrum of functions of secondary metabolites is much broader. They also serve as signaling substances to attract seed-pollinating animals, they protect other chemical constituents of plants from degradation by oxidative processes, or they safeguard plants from the detrimental effects of UV light from sun.

There is not only a remarkable biodiversity on earth with estimated

250,000 terrestrial plant species, the chemo diversity is much greater. The number of known chemical compounds from nature (excluding DNA-encoded proteins and peptides) has been estimated to be at least 200,000. Furthermore, only a minority of 15% of all plant species has been phytochemically analyzed thus far [10, 11].

The biological activities of secondary plant metabolites can be categorized in two groups: (1) those with a great selectivity for cellular targets and high bioactivity and (2) those with affinity to multiple targets and intermediate or weak bioactivities [12]. Many phytochemicals belong to the second category and act in multi-component mixtures. Cocktails of different phytochemicals may have selection advantages during evolution of life on earth, since they enable plants to protect themselves against a wide variety of predators without adapting specifically to them before a first encounter has taken place. Indeed, 90% of all thoroughly described medicinal plants contain broad spectrum compounds with rather moderate bioactivities [13]. They have pleiotropic activities and lead to measurable effects due to synergistic interactions [14]. Medicinal plants with highly active phytochemicals may represent only a minority. Another evolutionary advantage of phytochemicals with intermediate bioactivity is that highly active compounds might also harm their producing plants. In this case, plants have to develop specific protection strategies against their own weapons. One possibility is that the plant generates inactive pro-drugs that are activated only after uptake by the predator's metabolism. Another possibility is that inactive precursor molecules are produced that are matured to active compounds upon adequate stimuli. These molecules are interesting lead molecules for classical drug development. Prominent examples are the highly cytotoxic anti-cancer drugs vincristine and vinorelbine from *Catharanthus roseus*. Their precursors vindoline and cathatanthine are not or only weakly active [15].

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After Friedrich Sertümer isolated the first pharmacologically active natural product, morphine, from *Papaver somnifera* more than 200 years ago, chemicals from nature played an enormous role in pharmacology and pharmacy. The drug development process during the past half century demonstrated that drugs derived from natural resources represent a significant segment of the pharmaceutical market as compared to randomly synthesized compounds. In the 20th century, the discovery of penicillin initiated a mass screening of microorganisms for antibiotics. At the end of the 20th century 80% of all drugs were either natural products or derived from them in one or another way [16]. Of the 877 small molecule therapeutics introduced between 1981 and 2002 almost one half was a natural product, a semi-synthetic natural product analogue or a synthetic compound based on a pharmacophore derived from a natural product. It is estimated that about one quarter of all drugs in modern pharmacopoeias are derived from plants [17-19]. The isolation of novel bioactive phytochemicals and the systematic derivatization of these lead compounds from nature is the basis for the development of novel rationale drug therapies [20-26].

In addition to the pharmacological market in industrialized countries, as much as 80% of the population of developing countries even nowadays relies on medicinal plants as their only affordable source of medication [27].

Currently, phytotherapy is experiencing a revival in industrialized countries. One of the reasons for this growing popularity is a greater preference for natural products in comparison to chemical products. Herbal medicine is frequently looked upon as a gentle form of medicine without severe side effects. Although this might be true in many cases, it must not be overseen that the most toxic poisons are derived from nature. The evolutionary intention for the production of secondary metabolites is not to produce gentle medicines for human beings, but in contrast to defend from attacks by herbivores and microorganisms. The task of pharmaceutical and pharmacological research is to distinguish between toxic activities and pharmacologically valuable activities, which can be employed for therapeutic purposes. Performing safety assessments for drugs and chemicals have long been formidable issues in classical drug development [28]. Comparable safety measures have to be applied for herbal medicine. The ability to identify mechanism of toxicity of environmental toxicants or toxic contaminants of medicinal herbs represents a major requirement, if herbal medicine should regain global interest on international health markets.

Numerous examples for poisonous reactions of herbs have been documented in the literature [29-32]. A prominent case of herbal poisoning by aristolochic acids occurred in European countries in the 1990s. Herbal mixtures for slimming erroneously contained the poisonous *Aristolochia fangchi*, which contains the nephrotoxic and carcinogenic aristolochic acids [33-34]. Toxicity may not only occur by botanical misidentification or mix-up, but also by contaminations. Herbal products may be contaminated with microorganisms, fungal toxins such as aflatoxin, with pesticides and heavy metals, e.g. lead, cadmium, arsenic etc. [31]. Unprofessional processing, which differs from safe traditional preparation represents another potential source for herbal poisoning. Unwanted effects of herbal products may also develop by the interaction of herbs with conventional drugs upon concomitant intake [35].

Essential oils of aromatic plants

There is a progressive transition between food plants and medicinal plants and a clear distinction between categories is frequently not

possible. Plants primarily used for nutritional purposes may contain secondary metabolites with health promoting effects and even therapeutic potential [36]. Hence, it comes as no surprise that aromatic plants can also be medicinal plants, although their applications are much broader. These plants contain essential oils – volatile aroma compounds, which are isolated by distillation. Because the distilled oily extracts represent the “essence” of plants, they were termed essential oils. Essential oils have numerous usages in the “beauty industry” as perfumes, cosmetics, or soaps, in the food industry as flavors for foods and drinks, and in the medical industry. They have antiseptic, antimicrobial and antiviral activities [37-39]. As mosquito repellents, they bear the potential for malaria prevention [40]. Furthermore, they reveal considerable cytotoxicity towards cancer cells [41-43].

Essential oils of aromatic plants also play an important role in aromatherapy. This form of complementary and alternative medicine is used for the prevention and treatment of certain disorders. Two different modes of action have been suggested: One is directly related to the pharmacological effects of essential oils. The other relates more to the positive influence of aromatic substances on the limbic system of the brain via the olfactory system. The usefulness of aroma therapy for management of pain, anxiety, depression, hypertension etc. is discussed [44-49].

Future perspectives

Although research on medicinal and aromatic plants has a long-lasting tradition, there is a huge task for the future to fulfill the requirements and expectations on herbal health care for future generations. In addition to quality control standards, the modes of actions and synergistic interactions need to be much better understood. One of the possible pitfalls may be the right applications and indications need to be explored and improved in controlled clinical trials. Examples of future perspectives are the so-called neglected diseases, such as certain tropical diseases which are epidemiologically important, but seem not to justify private investments due to the lack of spending capacity in the respective countries. Detractors of herbal medicine argue that herbal medicines may be ineffective for such diseases. This assumption is fed by the fact that patients obviously take medicinal herbs against these widely distributed diseases, but treatment effects of medicinal herbs should be more obvious and neglected diseases should be under control by medicinal herbs if these would work. Obviously this seems not to be the case.

On the other side, there is mounting evidence that medicinal plants with their panoply of secondary metabolites reveal considerable activity against parasites causing neglected diseases [50-61]. This paradox illustrates the need for systematic research to improve and utilize the full potential of medicinal herbs.

Despite the fact that traditional medicine is trendy and booming nowadays (Figure 1) and despite the tremendous potential of medicinal and aromatic plants to combat diseases and disorders of mankind in the decades to come, there is a number of issues ranging from traditional knowledge on medicinal and aromatic plants to for a more globalized utilization in the future and to realize the full potential of medicinal and aromatic plants [62].

Overharvesting of medicinal and aromatic herbs from the wild may contribute to the extinction of such species. If indigenous people learn methods of controlled cultivation and harvest of medicinal and aromatic plants, sustained cultivation will not only secure the income of people, but also prohibit the extinction of endangered plant species. In

addition to plantations and greenhouse cultivation, the establishment of seed, germplasm and DNA banks may help to conserve endangered plant species. An intriguing example is China's first national seed bank for wild plants at the Kunming Institute of Botany which contains some 30,000 seeds (<http://www.bgci.org/resources/news/0716/>).

Medicinal and aromatic plants have to be correctly identified, since wrongly identified plants may contain poisonous ingredients. In addition to classical botanical identification of species and subspecies, authentication of medicinal plants by barcode DNA provides a novel and attractive technique, e.g. polymerase chain reaction-based methods based on variable sites of the rDNA internal transcribed spacer (ITS). These techniques do not only serve the correct identification of plant material, but are also used to conduct molecular taxonomy studies [63].

The quality of herbal and aromatic herbs largely differs among providers both regarding contents of phytochemicals and toxic contaminations. Therefore, standards for quality control are urgently needed. Herbal preparations should be produced according to international quality guidelines such as Good Sourcing Practice (GSP) to guarantee authentication of medicinal plants, Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), and Good Manufacturing Practice (GMP). The processing of herbal products should be standardized and the content of bioactive phytochemicals should be monitored by chromatographic fingerprinting analyses.

Another task of quality control is to avoid contaminations of herbal products with mycotoxins, pesticides, heavy metals, or other chemical toxins. Intentionally faked herbal prescriptions with adulteration of drugs from western medicine, e.g., with glucocorticoids or ACE inhibitors, have to be banned.

Another challenge for future research on medicinal and aromatic plants is the elucidation of the pleiotropic modes of actions of single ingredients of plants and even more of complex herbal mixtures. Recently emerging techniques of systems biology such as genomics, transcriptomics, metabolomics as well as their evaluation by bioinformatical tools represent a new area in medicinal and aromatic plant research [64-66]. This can be an effective approach for comprehensive evaluation of the effectiveness and qualities of medicinal and aromatic plants.

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