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From Pharmacognosia to DNA-Based Medicinal Plant Authentication – Pharmacognosy through the Centuries*

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ABSTRACT

For centuries, pharmacognosy was essential for the identification, quality, purity, and, until the end of the 18th century, even for the efficacy of medicinal plants. Since the 19th century, it concentrated on authenticity, purity, quality and the analysis of active substances, and was established as an academic branch discipline within pharmacy and continuously developed into a modern, highly sophisticated science. Even though the paradigm in pharmacy changed in the 19th century with the discovery of morphine and concentrated on single substances that could be synthesized fast by the upcoming industry, medicinal plants always remained an important element of the Materia medica, and during the last decades, medicinal plants continue to be a source of remedies, and natural products are an inspiration for new medicine. In this research, pharmacognostic skills remain an essential element, both with regards to identity, quality assurance of botanicals (both herbal medicines and supplements), and the discovery and development of new medicines. Over the years, the specific pharmacognostical tools have changed dramatically, and most recently, DNA-based techniques have become another element of our spectrum of scientific methods.

Introduction

Pharmacognosy has accompanied humans for millennia, and over centuries, it has developed traditions of evidence-based knowledge in cultures. It addresses both challenges relating to the supply of safe medicines and offers unique opportunities for modern drug discovery. The term will be used throughout the paper in the literal sense "the knowledge about medicinal drugs" and is not reduced to the definition of the academic discipline since the 19th century.

In this paper, we mainly focus on the history of pharmacognosy in Europe, being well aware of the fact that principally similar developments can be observed in many regions and cultures in the world which, metaphorically speaking, open unlimited horizons for research in pharmacognosy and drug discovery. Until the early 19th century, the *regnum vegetabile* or kingdom of plants was the most important and uncontested source for therapeutic agents in medicine and pharmacy.

As keeping and restoring health is doubtlessly an essential element of survival, it is not surprising that the knowledge about medicinal plants was highly appreciated as the famous botanist Augustin-Pyrame de Candolle (1778–1841) who stated: "Among all kinds of human knowledge, pharmacognosy is the most useful" and in 1909 the celebrated pharmacognosist Alexander Tschirch (1856–1939) considered it "eine wahre scientia regia", a real royal

* Dedicated to Professor Dr. Max Wichtl in recognition of his outstanding contribution to pharmacognostic and phytotherapy research.

science [1]. Yet, the ideas about the character, definition, and purpose of pharmacognosy changed over the centuries. While it comprised any knowledge about medicinal plants like identity, origin, habitat, morphology, medicinal properties, ways of application, methods of preparation, and adulterations from ancient times on, in the context of the differentiation of sciences since early modern time, it gradually developed into a science which mainly concentrated on identity, quality, and purity. Since the early modern age, one of the traditionally central parts of what later would be called pharmacognosy – the efficacy of medicinal plants which was always defined by the respective contemporary theoretical concepts like the Galenic humoral pathology – shifted into pharmacology. However, it has always remained a complex, ambitious science comprising various areas of expertise in many other scientific disciplines and today contributes again significantly to the exploration of the effects and efficacy of medicinal plants.

With the development of plant chemistry since the 18th century culminating in the isolation of morphine by the German apothecary Friedrich Wilhelm Adam Sertürner (1783–1841), the attention of pharmacy and medicine finally turned to single substances, their derivatives, and synthetic molecules that could be produced fast on an industrial level and were thought to be better controllable in dosage, efficacy, and side effects. In the progress of this development, many medicinal plants fell into oblivion, were not further investigated, or not even studied at all [2, 3].

Yet, medicinal plants and the knowledge about their identity, quality, purity, and efficacy have always remained an important element of medicine and pharmacy. There can be no doubt that M. Wichtl's Herbal Drugs and Phytomedicines, A Handbook for Practise on a Scientific Basis (German "Teedrogen und Phytopharmaka" with the 6th edition published in 2016 [5]) remains a core resource for the identification of herbal materials. It is unique and a true representation of traditional pharmacognosy in its best sense. It highlights the morphological and some basic phytochemical characteristics of important botanical drugs. At the same time, it is an area that has received little attention, and in the 21st century, few pharmaceutical scientists are trained in this field. As the name indicates, it is a practice-centered book and does not strive for incorporating the latest methodological innovations, but it is driven by practical usefulness. As another researcher in the field famously stated "Jeder Fortschritt in den Methoden ist auch ein Fortschritt in der Wissenschaft" (Egon Stahl: 'Every progress in methods also is a progress in science'), over the last two hundred years the approaches and methods in this field have changed dramatically and continue to do so [6]. There have been numerous reviews assessing specific developments in this field of research (e.g., [6–8], which has also been covered in a wide range of textbooks, e.g., Trease and Evan's Pharmacognosy [9] and [10–12] as well as, for example, German language textbooks such as [13, 14]).

During the last decades, scientific interest has turned again to medicinal plants as research to their traditional uses, compounds, pharmacology, and composition might reveal new opportunities for the future challenges and essential medical needs, not only under the aspect of "soft therapeutics" but also as a source of highly effective resources for the treatment of serious diseases with presently unsatisfying therapeutic solutions. Today we have new methods and much more knowledge to explore the composition of plants under the aspect of their efficacy much deeper than ever and can now link this to pharmacological and clinical studies, allowing a much better understanding of herbal medicines. In this development, pharmacognosy will be a central and irreplaceable science and cover further essential fields of investigation.

Millennia of Experience and Tradition – The Scientia Regia

The knowledge about the identity, quality, properties, and uses of medicinal plants was developed over thousands of years in a process of evidence-based experience, exchange of expertise, and the forming of a complex tradition, which nowadays can be explored by the methods and instruments of modern science.

While ancient cultures around the globe had gathered and adopted knowledge about the healing properties of medicinal plants and handed it down, enriched by further developing knowledge and evidence-based experiences, from generation to generation, in Europe, it was the famous work *De materia medica* written by the Greek physician Dioscorides (1st c.) that probably became the most influential work for forming and transmitting pharmacognostic knowledge. Dioscorides is said to have been a physician of the Roman army accompanying them during their conquest campaigns around the Mediterranean regions, and by this exploring the medicinal potency of the local florae. He recorded more than 800 plants and their products, giving information about their vernacular names, provenance, morphology, medicinal properties, and medical-pharmaceutical applicability. He even mentioned criteria to differentiate between the genuine drugs and potential adulterations. For the systematic presentation, the completeness of knowledge, and the evidence-based information, for more than 1500 year this work determined the perception and concept of pharmacognosy in Europe. In the following centuries, it appeared in innumerable editions and adapted versions, among them the famous *Anicia Juliana Codex* or *Vienna Dioscorides* (512 AD), which is illustrated by sophisticated depictions of plants and today is kept in the Austrian National Library under the signature Cod. med. gr.1. The impressive illustrations of this codex reveal the high book art and admirable book illustration in the Byzantine period. The codex became a model for numerous herbals of the middle age and the beginning of early modern time [15, 16]. Many medicinal plants of Disocorides' work *De materia medica* are still today important therapeutics of our Materia medica [17, 18].

The European tradition, however, was also influenced by continuous intercultural exchange via the great trade routes, travel, and commerce. Origins of such knowledge were, for example, the Ayurvedic body of knowledge containing the ancient and complex Indian system of medicine represented by famous works like the *Carakasamhitā* (1st c. BC-2nd c. AD) and the *Suśrutasamhitā* (early 3rd to early 6th c.), which comprise explanations of hundreds of medicinal plants and their application [19]. In China, the so-called *Pen-t'sao* literature reflected centuries of experience

and tradition in the application of medicinal plants. The work *Shen-nung's Pen-Ts'ao ching* (Shen-nung's classics on pharmaceutics, anonymous, later Han dynasty 23/25–220 AD) offered information and comments on more than 300 medicinal plants used in classic Chinese medicine [20].

From the late 7th century onward, Arabic-Islamic scholars played an essential role as intermediaries in the transfer of knowledge between the classic antiquity and Latin Europe. Highly interested in science and exploration, these Arabic scholars started to translate the extant original Greek works and also translations in other languages like Syrian into Arabic and, consequently, provided a solid fundament for further scientific development. However, such activities were far from being plain translations and copying, but the Arabic-Islamic scholars enriched the classical pharmacognostic knowledge with traditional and local empirical knowledge, their own ideas, and expertise from experience. At the same time, the Arabs maintained intense trade relations and were connected to the contemporary great trade routes like the Silk Road and the Incense Road. In addition, the Arabic empire expanded widely to the Middle East, North Africa, and to Western Europe, mainly the Iberian Peninsula, which led into intense contact with different cultures and a mutual participation in expertise. Through these routes, medicinal plants, for example, from the Indo-Iranian, Syrian, Afghan, Chinese, and Indian traditions including information about medicinal indications and applications, were integrated into the Arabian Materia medica. Similarly, medicinal plants from the Iberian Peninsula made an important contribution to the further formation of medieval pharmacognostic knowledge. The scientific potential of the pharmacognosy during the medieval Arabic-Islamic period is reflected in the general medical literature containing comprehensive information about the characteristics and use of medicinal plants, such as the works by Rhazes (865–925), Ibn Sina (980–1037) also known as Avicenna, and Ibn al-Ǧazzar (died approx. 1004), or explicitly pharmacognostic works, for example, the *Kitāb al-Ŷāmi' li-mufradāt al-adwiya wa-l-agdiya* written by Ibn al-Baytâr (around 1190–1248), the *Kitāb al-adwiya al-mufrada* by Ibn Wāfid (999-app.1068), and the *Kitāb fī l-adwiya al-mufrada* by Al-Ghâfiqî (died 1165). This comprehensive medical and pharmacognostic lore was delivered to Europe by Latin translations and formed the fundament for the further development of pharmacognosy in Europe [21–23].

In the process of forming pharmacognostic knowledge in Latin Europe, the ancient lines of tradition merged with European lines of transmitting knowledge such as the monastic pharmacy, the tradition of the School of Salerno, and popular expertise represented by works like the *Macer floridus* (between 1080 and 1100), probably written by the cleric Odo von Meung, and the *Circa instans* and the *Gart der gesuntheit* (1485) by Johann Wonnecke von der Kaub (1430–1503/04). This corpus of medieval pharmacognostic expertise formed the foundation for the further development of knowledge about the properties of medicinal plants in Europe [16, 24].

In the early modern period (16th-17th century), the great herbals presented and transmitted the pharmacobotanical knowledge such as the *Kreütterbuch* (1539) by Hieronymus Bock (1498–1554), the various editions of the *Kreutterbuch* by Pietro Andrea Mattioli (1501–1577), and the different editions of the *Neuw vollkommentlich Kreuterbuch* by Tabernaemontanus (1525–1590). In the context of the European expansion, new exotic drugs were brought to Europe, and the pharmacognostic knowledge about these medicinal plants was integrated into the development of European traditions [3]. Pharmacognostic expertise became even more essential to identify drugs as well as their origin, efficacy, purity, and adulterations. Special works about the Materia medica and pharmacopoeias reflect the contemporary difficulties and efforts to guarantee these basic requirements.

While the differentiation and formation of modern sciences started in early modern time, in the academic curriculum in the 16th century, pharmacognosy, as actually one of the oldest sciences, remained initially a plain subject at the Faculty of Medicine first taught as *Lectura simplicum* (lecture about the simples) accompanied by the *Ostensio simplicium* (presentation of the simples), and afterwards as *Materia medica* (lecture about medicinal drugs) [1]. Only in the 18th century did pharmacognosy start to develop into a defined academic branch discipline in pharmacy.

While physicians, botanists, and pharmacists like Johann Adam Schmidt (1759–1809), who is credited with defining the term 'pharmacognosy' in his posthumously published work *Lehrbuch der Materia Medica* (1811), Theodor Wilhelm Christian Martius (1796–1863), and Matthias Schleiden 1804–1881) paved the way for the differentiation of pharmacognosy into an academic discipline, it was the Swiss apothecary Friedrich August Flückiger (1828–1894) and finally the famous German apothecary Alexander Tschirch (1856–1939) who at the turn of the 20th century perfected the definition and perception of pharmacognosy [25]. Tschirch explained pharmacognosy as a universal synopsis of the medicinal drugs considering any type of knowledge necessary for identification and characterization, except the physiological efficacy, and defined special disciplines that he considered to be essential for forming such comprehensive knowledge: *Pharmakoërgasie* (cultivation, harvesting, processing of harvested material), *Pharmakoëmporia* (trade routes, export and import ports, processing of drugs in the import ports), *Pharmakodiakosmie* (traded varieties, packaging), *Pharmakobotanik* (botany, systematics, morphology, anatomy, physiology, pathology), *Pharmakozoologie* (zoology, systematics, morphology, anatomy, physiology, pathology), *Pharmakochemie* (chemistry of drugs), *Pharmakophysik* (physics of drugs), *Pharmakogeografie* (geography of drugs), *Pharmakohistoria* (history of drugs), *Pharmakoethnologie* (ethnology of drugs), and *Pharmakoetymologie* (etymology of drug names) [1]. While Tschirch's predecessors already had emphasized the multidisciplinary character of pharmacognosy, Tschirch went a step further and stated that the main chemical compounds determined the nature and medical properties of medicinal drugs and therefore built the connection between the drugs to characterize them accordingly, e.g., saponine-, alkaloid-, and anthraquinone-containing drugs. Defining medicinal drugs for the first time by their chemical compounds, Tschirch paved the way for pharmacognosy as a modern science and developed the "knowledge of drugs (*Drogenkunde*) into a science of drugs (*Drogenwissenschaft*)" [1, 26]. In this context, Tschirch postulated that the *pharmacochemistry* had to explore all compounds of a drug as "the efficacy of a drugs is rarely caused by only one compound but mostly by the composition of the compounds" [Die Pharmakochemie (muss) „das En-

semble möglichst aller Bestandteile kennen lehren, denn die Wirkung der Droge ist nur selten das Korrelat eines Bestandteils, und meist eine Mischwirkung."]. This opinion obviously did not follow the contemporary scientific mainstream, which considered single compounds to be the best therapeutic solutions.

However, Alexander Tschirch's impressive achievements and innovative research approaches did not lead to intense research efforts in exploring the properties and potential therapeutic use of medicinal plants even though pharmacognosy was well established in the academic curriculum of the pharmaceutical branch disciplines in many countries, with the exception of Germany, a fact which was often criticized and discussed [25].

It took decades until his concept of exploring the chemical compounds was intensely developed by researchers like Kurt Mothes (1900–1983) in Halle, Germany, who included plant physiology, biochemistry, isotope technology, and biosynthesis into his research program and Richard Wasicky (1884–1970), who is a representative for the scientific pharmacognosy in Austria [27, 28].

There is ample historical evidence that the concentration on the application of single substances in drug discovery and development pushed plants as multi-compound mixtures into the background. This was driven by the expectation that this made it easier to control dosage and efficacy and, most importantly, that such medicines could be produced in large amounts at a low price in the growing pharmaceutical and chemical industries to satisfy the needs. This is exemplified by highly effective substances like the Camptothecin derivatives from *Camptotheca acuminata* Decne., the vinca alkaloids from *Catharanthus roseus* (L.) G. Don, or taxanes from *Taxus brevifolia* Nutt.

The challenges of investigating the complexity of the composition, efficacy, synergistic effects, and the adequate dosages could not be met by the analytical technical tools of the period. Neither did the state of knowledge in related sciences like biochemistry, pharmacology, biotechnology, and genetics research allow fruitful research on such complex mixtures.

With the large number of unsatisfied needs and future challenges in medical therapy, plants as multi-compound mixtures have gained new attention as potential therapeutic agents. The immense knowledge in many scientific fields accompanied by adequate analytical-technical approaches offers unique possibilities to explore medicinal plants that have been used over centuries again based on empirical evidence and make them available in modern therapies. This means, as outlined in the following section, more detailed studies in analytics, efficacy, synergistic effects, and clinical applications are necessary and it is also essential to reconsider the present regulatory framework and its applicability for the registration of phytotherapeutics and plant-based medicines.

Pharmacognosy Today – Analytical and Regulatory Challenges

The focus on complex mixtures remains a core interest of modern pharmacognosy, and in a very general way, it can be divided into two lines of activities, thus expanding and modifying the original focus (see above): The identification and authentication of drug substances and the quality of the resulting medicines, and the search for new medicines, their production, and research into understanding their pharmacological (including toxicological) effects and their effectiveness.

Clearly, the first very much follows the classical definitions as laid out above. These aspects of the field were developed at a moment in history when complex preparations derived from natural sources still were the only source of medicines. Today, a very diverse set of pharmacognostic methods is available, including microscopic [5], phytochemical [29], and genetic [30] techniques. Here we do not have the space for specifically reviewing such techniques, but we will highlight these changing approaches and the importance of the regulatory framework in defining best practice.

With regards to drug substances, their quality, and analysis, and using *Hypericum perforatum* L. (St. John's Wort) as an example, Agapouda et al. [31] reviewed the quality control of *H. perforatum.* This species is one of the most commonly used ones and a large number of herbal medical preparations are used, with many being licensed or registered, most importantly, for treating minor or moderate forms of depression and a range of mood disorders. In 2008, a Cochrane review evaluated 29 randomized double-blind trials (5489 patients with mild to moderately severe depression) found SJW extracts to be superior to placebo, with a similar effectiveness to standard antidepressants, but with fewer side effects [32]. A huge number of experimental methods are available, with TLC and HPTLC being the basic methods in the routine approaches. HPLC-DAD is the most widely applied method for quantitative analysis with a high degree of versatility. Near infrared spectroscopy is important in industrial practice. Very sensitive LC-MS-based methods are becoming more important, especially in pharmacokinetic studies. Other approaches, such as DNA barcoding and NMR metabolomics, are currently not accepted as validated methods, but offer new opportunities, and while they may not use the term "pharmacognosy", all of these methods are used with, in essence, the same objectives as they were defined by Alexander Tschirch and his predecessors, that is to ascertain the authenticity and quality of the herbal substance and the products derived from it.

DNA barcoding is making an important contribution to understanding not only the quality, but the systematic complexity of the species and its relatives. DNA barcoding uses small and well-defined DNA sequences in the plants' genome as a distinctive characteristic, allowing for a species' identification. The methodology was, of course, developed in the context of genetic research, and in botany, it plays a key role in plant systematics becoming an important tool, not only for specimen identification, but also resulting in significant advances in systematics, allowing a much better understanding of the relationship between taxa. In the last years, it has also been embraced as a tool to authenticate botanical drugs at the species level (i.e., it cannot be used to identify a botanical drug but only the taxon it is derived from).

For example, *H. perforatum* L. has, in recent years, attracted considerable interest, both from the perspective of plant systematics as well as medicinal plant authentication (i.e., pharmacognosy). The taxon has a complex history of recurrent poly-

ploidization and gene flow between *H. perforatum* and *Hypericum maculatum* Crantz [33, 34]. Morphological and chromosome data point to the possibility that *H. perforatum* L. could be a hybrid of *Hypericum attenuatum* Fisch. ex Choisy and *H. maculatum*. Specifically, ITS1 and ITS2 sequence data [35] allowed a clear distinction from important related species including *H. maculatum*, one of the potential parent species of the assumed hybrid. While this has allowed for great progress in our understanding of genus' systematics, its use in a more regulated environment, like the authentication of medicinal plants, requires further research and development.

The first routine methods, which could be used to clearly distinguish the pharmaceutically used species from other ones, were published in 2017. A first general DNA-based method was incorporated into the British Pharmacopoeia using *Ocimum tenuiflorum* L. or tulsi as an example [36].

Clearly, it will allow the identification of genetically distinct material in a botanical drug, but the limitations of the approach are multifold. It is one of many techniques used to define the composition and quality of a botanical drug and of extracts derived from it. Obviously, all DNA-based methods also are indirect methods in the sense that they do not allow to identify or even quantify the active metabolites in the plant or its preparations. The most important limitation is clearly that, in general, it can only be used on unprocessed drug material and not with extracts and after any other process that results in the degradation of the DNA. While opportunities for DNA barcoding with processed materials are actively being explored (e.g., amplicon metabarcoding – AMB), methods that can be incorporated into a pharmacopoeia for such materials still will require considerable research and development. The complexity of species and the species concept need to be taken into consideration [e.g., in complex species (aggregates), especially in taxa where apomixis and polyploidy are common]. Consequently, one will always have to rely on a combination of methods.

In our context it does highlight that all of these methods contribute to the *cognosis* or identification of the *pharmacon* or the drug substance. As pointed out by Parveen et al. [30], among others, in general, a combination of methods will be needed for the "successful authentication of botanical ingredients". There are few drugs for which such a detailed set of analytical techniques is available, and depending on the breadth of the definition of a medicinal (and health food) plant for thousands and more species, there is a need to develop such pharmacognostical techniques. Clearly, a limit will have to be drawn and this must be based on the relevance of these species in national and international trade networks.

While in this context pharmacognosy remains essentially an analytical science, it is also embedded in the specific regulatory framework of a country or regions. Lack of quality control is common and the resulting problems with adulteration and poor quality have come into the focus of discussion. This has been identified in numerous countries including the USA (see below), Japan [37], and Europe [38]. Such problems are commonly linked with unregulated or poorly (self-)regulated products and very often with so-called lifestyle drugs (antiaging, slimming, aphrodisiacs, e.g., [38]). Since 2011 (St. Gaffner, pers comm, 04/01/2017), in the USA, three non-profit organizations, the American Botanical Council (ABC), the American Herbal Pharmacopoeia (AHP), and the University of Mississippi's National Center for Natural Products Research (NCNPR), have been running a large-scale program on ingredient and product adulteration and the associated risk, with the specific goal to engage the relevant stakeholders in ascertaining best practice (see http://cms.herbalgram.org/BAP/index.html?ts=1475004575&signature=ed71dcf23c2084b-ba78071bddd2a0b38).

Already at the time of Alexander Tschirch, a global trade in botanical materials for medical use existed and today this trade has increased incrementally, highlighting the need for a better understanding of the global trade networks (value chains) and how these impact both the livelihood of primary producers and the resulting challenges for ascertaining best quality [38, 39] While there have been tremendous advances in a wide range of analytical techniques, including hyphenated ones [29, 40], the core methods required in routine quality control must be robust, fast, and highly economical (both in terms of time and equipment).

The above defines a crucial set of pharmacognostical tasks and while it may not be an area that results in highly influential publications, it is essential in setting industrial standards. At the same time, the fast development of ever more sensitive and advanced techniques offers opportunities that are relevant in the context of the second major area within pharmacognosy: The search for new medicines, their production, and research into understanding their pharmacological (including toxicological) effects and their effectiveness [41]; see also [42].

In taking such a wider perspective, numerous other methods come into play, including the diverse methods of isolation, pharmacological and clinical investigation as well as the associated pharmacovigilance schemes. Clearly, all were developed well after the initial definition of the field of pharmacognosy, which until the second half of 20th century relied on the observation of effects of preparations when applied to humans and animals. Interestingly, during the process of defining the concept of pharmacognosy (see above for the work of J. A. Schmidt and others) of the 19th century, morphine from *Papaver somniferum* L. (Papaveracae) had already been identified by Friedrich Wilhelm Sertürner in 1804, and in 1817, was chemically characterized as an alkaloid. Over 100 years later, in 1923 in Manchester, Gulland and Robinson established its full structure. Drug discovery from natural sources continues to yield exciting new drug leads [10–12] and research today is embedded in complex regulations of best practice, including the recognition of the rights of the provider (countries) (Bauer et al., forthcoming). Recently, the plant-derived natural products galanthamine and Peplin/ingenol-3-angelate [43] have become important new medicines. Plant-derived anticancer agents remain core therapeutic options, e.g., [44], and numerous fungal metabolites have been developed or are under development [45]. These techniques also lead to the need for the major development of bioinformatics and related techniques. One can argue that these areas no longer should be included under the heading of pharmacognosy in a strict sense, but even then one will have to acknowledge that pharmacognosy is the origin of all these disciplines and research activities.

Conclusion

Today, pharmacognosy faces numerous challenges and at the same time offers many opportunities. Identification and authentication of nature-derived products have been a continuous core challenge and will remain an important competence. Clearly, new methods are required for this and, as such, DNA-based techniques are simply an addition to the wide range of tools used in this context, and they are an exciting opportunity. Here we wanted to show the *conceptual continuum and the constant incorporation of new methods into a medical-pharmaceutical science*. In addition, pharmacognosy nowadays has the unique opportunity to explore further fields of investigation, especially in drug discovery and clinical development, and by this, return to its origins of a complex and comprehensive science for both medicine and pharmacy [46].

Century-old traditions in all cultures reflect an immense knowledge of medicinal plant use, which is reflected by innumerable historical sources. This fact has been commonly accepted and dealt with in many publications with comprehensive bibliographies [4, 47]. However, many methods to explore this potential did not lead to convincing results, especially if historical indications were directly correlated to modern applications or if the authors concentrated on a single defined species. Recent studies in the history of pharmacy present methods and concepts to analyze historical traditions in detail, evaluate them according to modern scientific knowledge, and link the results directly to the scientific research of the pharmaceutical branch disciplines like pharmacognosy, chemistry, and pharmacology to lead to a complete drug development [4, 48–50].

Millennia of experience in evidence-based applications of innumerable medicinal plants used in all cultures wait to be analyzed, explored, and made available for modern therapy, be it as multi-compound pleiotropic preparations (herbal medical products/botanicals) or as pure natural products [2, 5] and, of course, based on the modern legal frameworks including the Convention on Biological Diversity [10, 11, 42, 43] and subsequent treaties. Already Tschirch recognized the value of historical traditions and the potential for discovering mixtures or substances with a potential for wider use. Specifically, his concept of the synergistic efficacy of all compounds of a plant extract should be studied further in the context of understanding the implications for efficacy. While Tschirch did not have the methodological and instrumental equipment to investigate the different preparations, their respective profiles and fingerprints, their clinical efficacy, and the necessary modifications and dosages, we can explore this wide and still little known field as another core competence of pharmacognosy.

The analytical power of modern hyphenated techniques and the opportunities of DNA barcoding provide great opportunities for a much better understanding of complex preparations and give a new impetus to pharmacognostic research approaches. A key challenge will be the large number of local and traditional medicines used and traded in, and from biodiversity-rich countries with a long and strong tradition of using herbal medicines, especially from Asian countries like China, Thailand, and India, but also from American and African countries. It can be predicted with certainty that this trade will continue to increase and there will be an increased need for pharmacognostical-analytical tools to assess the authenticity and quality of these products.

Pharmacognosy combines rich historical traditions and millennia of evidence-based knowledge with the expertise and skills of modern science and, therefore, is an irreplaceable and promising science for drug discovery and the development of modern drugs. In the future, it may even be a new medical-pharmaceutical paradigm that could focus on multi-compound mixtures as therapeutics in an adapted regulatory framework.

We would like to close with some contemplative thoughts by the famous and renowned pharmacist and pharmacognosist Franz Christian Czygan (1934–2012). In 1984, he wondered whether the exploration of medicinal plants had been neglected for such a long time that the clock already showed five after twelve. While concentrating on the smallest details, we lose the view for the whole, and therefore so many plants and other natural sources such as marine organisms, including their compounds, on our planet have not been explored, which could offer an immense potential of therapeutic options. Therefore, it is our responsibility as scientists to preserve and investigate plants and further natural sources as a heritage and for the benefit of humankind [46].

Conflict of Interest

The authors declare to have no conflict of interest. Sponsors of our research have had no influence on this paper.

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