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Herbal medicinal products – Evidence and tradition from a historical perspective

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ABSTRACT

Background: Aside from the fully licensed herbal medicines there are products on the European pharmaceutical market which are registered by virtue of their longstanding traditional use. The normal registration procedure does not apply to them because presently they do not meet the legal requirements for a full license as set out in the relevant European Union Directive. One of these requirements, "proof of tradition", has so far been dealt with in different ways and fails to meet the criteria of *good practice*.
Method: This analysis is based on a selective literature search in PubMed and in databases of medical and pharmaceutical history, interviews with licensing experts, a consensus meeting attended by researchers with a background in general medicine, phytotherapy, medical and pharmaceutical history, biometry, ethnopharmacology, pharmacognosy and the pharmaceutical industry.
Results and discussion: The 2004 EU Directive, which governs the registration of Traditional Herbal Medicinal Products and demands proof of tradition, is a regulatory construct and, above all, the outcome of a political process that has ended in a pragmatic compromise. The concept of tradition applied in the Directive does not sufficiently reflect the semantic breadth of the term. The only condition defined is that a specific commercial preparation needs to have been on the market for 30 years (15 of them inside the EU). Such an approach does not make full scientific use of the evidence available because the information excerpted from historical sources, if adequately processed, may yield valuable insights. This applies to indications, modes of application, efficacy and product safety (innocuousness). Such criteria should enter in full into the benefit-risk-analysis of applied preparations, in the registration process as well as in the therapeutic practice.
Conclusion: When registering Traditional Herbal Medicinal Products the criterion of evidence-based medicine will only be met if all the facts available are assessed and evaluated, over and above the formally stipulated regulatory provisions (30 years, product reference). To this end, the scientific methods (from among the natural, life or cultural sciences), which are recognized as authoritative in each case, must be applied.

1. Introduction

In many countries of the EU and beyond (e.g. Australia), herbal medicines are used based on a tradition of use. For example, seventy per cent of German people have used 'natural medicines' (Allensbach Survey, 2017) with herbal preparations being the most commonly used type. In Germany alone, herbal medicines worth 1.36 billion market data were sold in 2015 without prescription, by mail order or in pharmacies (IMS Health OTC® Report, 2015). Aside from the fully licensed medicines, there are also products which are registered as

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traditional medicines on the strength of their longstanding use. In the context of ethnopharmacology, this poses some core challenges, most importantly with regards to how to build an evidence-base for the use of such products specifically with regards to defining what constitutes a tradition of use as a medicine.

2. Regulatory procedures and proof of efficacy

In 2004 a European Union Directive (Directive, 2004/24/EG) was passed in order to address the growing demand for Traditional Herbal Medicinal Products (THMP), which do not fall within the scope of the normal regulatory procedure because they do not provide the proof of efficacy that is legally required for a full license, and also in order to "ensure the greatest possible protection of public health" (Stellungnahme, 2003), as requested in a statement of the Economic and Social Committee of the European Parliament. Today, the European Union member states use this Directive as a guideline for registering herbal medicines for self-medication. These herbal medicines must have a sufficiently established tradition and be proven to be safe enough to be placed on the over-the-counter (OTC) market (Vlietinck et al., 2009). Concrete evidence must be provided for the product not being "harmful in specified conditions of use and that the pharmacological effects and the efficacy of the medicinal product are plausible on the basis of longstanding use and experience". As part of such evidence "proof of tradition" needs to be supplied, which Article 16c (1c) defines as "bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the Community [i.e. within the European Union]".

Since 2004, this European Directive has been incorporated into the national legislations of the EU member states. In the Federal Republic of Germany, for instance, the clause is almost literally included in Section 39b of the Medicinal Products Act (*Arzneimittelgesetz*, AMG, cf. notification of 12/12/2005): "Applicants are required to submit with their application for registration the following information and documentation; [...] 4) bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product, has – at the time of application – been in medicinal or veterinary-medical use throughout a period of at least 30 years, including at least 15 years within the European Union, that the medicinal product is not harmful in specified conditions of use and that the pharmacological effects and the efficacy of the medicinal product are plausible on the basis of longstanding use and experience" (Arzneimittelgesetz, 2005).

This regulatory construct (including the timeframe it specifies) is primarily the result of a political process and, therefore, constitutes a pragmatic compromise. It reflects the efforts at EU-level to create a harmonized legal framework for this section of the medicines market, too. However, the Directive uses a concept of *tradition* which fails to reflect the complex semantic breadth of the term and, therefore, does not fully exploit the scientific evidence available. With this article, we demonstrate how – using the appropriate scientific methods – this can be resolved and how additional evidence can be created as a result. The arguments in the paper are relevant both in the context of ascertaining best practice in the use of herbal medicines, but also are of wider relevance in the context of ethnopharmacology, exemplifying problems with how such uses are labelled as 'traditional'.

3. A vague concept of tradition

The concept of "traditional use" is not explained anywhere in the legal provisions. The law itself merely defines criteria that need to be met if medicines are to be registered as a THMP, such as the apparently arbitrary temporal specification ("at least 30 years, including at least 15 years in the European Union"). The main underlying intention was, it seems, to harmonize for the Common Market the various traditions of use applied for herbal medicines in Europe – based on the criteria of longstanding and, above all, safe use (Kügel et al., 2016, 707). As is apparent from the relevant legal commentary, the required form and content of such documentation, therefore, are subject to legal requirements (Kloesel and Cyran, 2004, 124).

The multiple layers of a concept as colourful as "tradition" have, so far, not been taken into consideration. In view of the semantic problems raised by this concept, especially in the medical context, it seems appropriate briefly look at the way the term is used in other disciplines (sociology, anthropology, history and philosophy) in order to gain insights for using it in the context of medicine.

In *sociology* above all the work of Edward Shils (1910–1995) needs to be mentioned. For Shils, tradition is primarily a formal process of transmission ("anything which is transmitted or handed down from the past to the present" (Shils, 1981, 12)). This process can involve material objects as well as practices. The decisive factor is that they have been or are being transmitted. According to Shils, an industrial production process in itself (this applies also to the manufacture and marketing of a medicinal product at an earlier point in time) does not yet create a tradition; for it to become tradition the process needs to be transmitted, or ritualized. Repetition, or "re-enactment", is consequently an indispensable precondition for tradition. Transmission has to proceed in several stages and, as a rule, cover two to three generations (Shils, 1981, 16; Weick, 1995, 124).

From among the many *ethnological* theories the approach introduced by Richard Handler and Jocelyn Linnekin are particularly relevant to our context. Both of them see tradition as symbolic construction and representation. Tradition, in their view, does not simply mean handing down. It involves initial construction followed by continual transformation through interpretation. Handler and Linnekin speak of a "paradox of tradition" (Handler and Linnekin, 1984). Tradition can also be "invented", as Eric Hobsbawm (1917–2012) and Terence Ranger (1929–2015) demonstrate in their ideology-critical studies (Hobsbawm and Ranger, 1992). The most accessible example of an invented tradition are folk garments. Such costumes are not time-honoured traditions but rather a nineteenth century phenomenon. They are not examples of what farmers used to wear for work or for festive occasions but reflect the interest of city-dwellers in the rural population and its customs.

In *history* the term "tradition" has been used since Johann Gustav Droysen (1808–1884) to describe the conscious transmission of contents, for instance in memoirs or other ego-documents (Brandt, 1958, 56ff.). These need to be differentiated from "remnants", which are unintentionally passed-down testimonials of historical occurrences, such as legal or everyday texts, buildings, objects, but also abstract documents of human coexistence such as language, customs and rituals. This differentiation, as will be explained below, is particularly important when it comes to historical evidence (for example a critical assessment of sources).

Even more relevant to our regulatory context is the concept of "social validation" advanced by John K. Crellin, the Canadian historian of medicine and pharmacy, in order to define the tradition of complementary-medical therapies more precisely. According to Crellin, a tradition is "the more valid" the further it can be traced into the present and the more ubiquitous it is in geographically separate regions. Other factors, such as the usefulness experienced by patients, also inform this matrix of evaluation (Crellin, 2001).

Philosophers, too, have given thought to the concept of tradition. According to Hans Blumenberg (1920–1996) a tradition does not consist of "relics, but of attestations and legacies" (Blumenberg, 1981, 375). In other words, tradition does not refer to some remnants of the past nor does it emerge by itself but through inheritance or affirmation (Assmann, 1994). Such a cultural inheritance, which is passed down from generation to generation, can comprise scientific knowledge and workmanship as well as artistic conceptions, behaviours and values. Another philosophical approach derives from Jürgen Habermas' Theory of Communicative Action (Dittmann, 2004, 323ff.). In order

to resolve the relatively common problem of contradicting traditions, communicative methods can be employed that allow everyone involved to participate in the process of conflict resolution. Karl Popper (1902–1994) was the first to establish a rational foundation for tradition (Popper, 1972). Starting from the idea of the "*living tradition*", it also offers a solution to the problem of authenticity (Beckstein, 2017).

Even though the humanities and social sciences have differing concepts of tradition, these concepts tend to have one characteristic in common: If the concept is to be meaningful at all, a tradition, in the sense of a cultural inheritance, must take account of social dynamics and, therefore, span at least two generations. Assuming a generational interval of 30 years amounts one would have to take 60 years as a minimum, a very long period in today's progress-oriented medicine. Therefore, it has not found access into the EU Directive on THMP or the subsequent German Medicinal Act. However, (medical-)ethnological research as well as pharmacological research, which is influenced by the former, point to the need to consider longer periods of time, even if such a consideration does not amount to proof of tradition under the medicinal regulation. For example, the 2015 Nobel Prize for Medicine which was awarded to the Chinese scientist Youyou Tu based on a discovery linked to meticulous botanical-historical research (Tu, 2016; Unschuld, 2015). In the 1960s Ms Tu and her colleagues began to search the ancient Chinese literature for references to substances which have proven effects in cases of malaria. They first selected from the numerous historical sources a large number of medicinal plants, including *Artemisia annua L.* The annual common wormwood was first mentioned for the treatment of malaria in the recipe collection of the renowned Chinese scholar Ge Hong (284–364 C.E.), and this specific application is documented again and again over a period of almost 1700 years. The Chinese research team also discovered essential references in this source to the extraction procedure and, therefore, to the isolation of the active metabolite artemisinine. Clinical studies provided positive proof of the substance's efficacy. Today, artemisinin is a clinically essential antimalarial medicine uses throughout Asia, Africa, and Southern America.

The terminology used in the EU Directive – or in the German Medicines Act – does not necessarily conform to (nor is it required to in this context) the concept of tradition used by the World Health Organization (WHO): "Traditional medicine is the sum total of knowledge, skills and practices based on theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses" (WHO Traditional Medicine Strategy 2014–2023). This definition refers to culture-specific medical systems with traditions going back hundreds if not thousands of years (in China or India, for instance) and coincides with the commonly accepted interpretation of tradition as culturally inherited. The ethnopharmacological studies underlying these concepts have, however, rarely been subjected to historical scrutiny. Instead, "traditional medicine" is equated one-sidedly and synchronously with the forms of therapy practised locally and in the present (Heinrich, 2006; Lardos, 2015). Often this interpretation is limited to orally transmitted traditions, even if these have been influenced by written traditions for hundreds of years (Leonti, 2011).

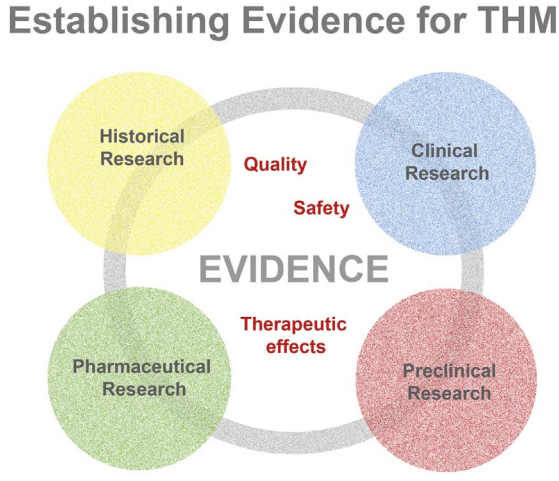

Fig. 1. Establishing evidence for THMP.

4. Problems in regulatory practice

The development of the "proof of tradition" is represented within the framework of the THMP registration is shown in the Assessment Reports of the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA). These reports form the basis of the corresponding HMPC-Monographs and together help the EU member states to harmonize their – subsequently largely autonomous –decisions on a specific registration. They also contain reference lists and, therefore, in each case reflect the underlying scientific state of knowledge.

If one scans these Assessment Reports, it emerges that a part of the evidence available has been systematically omitted. The inclusion of all potentially available sources and their methodically and conceptually adequate appraisal can yield important new evidence for clinical application, however, with consequences for the therapeutic practice and the use of herbal medicines. Otherwise, the concept of "traditional use" could, for example, easily be misinterpreted as demonstrating a lack of evidence (Fig. 1)

Using the example of the monographs approved by the National Health Products Directorate (NHPD) in Canada, John K. Crellin has impressively demonstrated the consequences that can ensue when literary references taken from older pharmacopoeias or other pharmaceutical reference sources are used inconsistently or adopted without scrutiny for developing Assessment Reports on traditional herbal medicinal products (Crellin, 2008). Similarly, the findings of Klose et al. reveal problems in the safety assessment if sources from diverse medical and pharmaceutical contexts are used without careful differentiation (Klose et al., 2016). The regular review and updating of HMPC monographs every five years does not resolve the fundamental problem of historical evidence (or in this case the lack thereof) unless such omissions are rectified in each case.

The registration practice applied so far has shown, moreover, that the "proof of tradition"-aspect is dealt with differently in each of the member states. Reasons for this include the vague wording in the regulation and the problems linked to the concept of plausibility essential in the context of safety and efficacy, and linked with the attributes "traditional" or "longstanding" (Heinrich, 2015).

The specified period of at least 30 years for proof of tradition is entirely arbitrary (Moreira et al., 2014; Australian Government, 2014). In practice this period often proves to be either too short or too long, depending on whether it refers to herbal medicines, herbal substances or herbal preparations. This randomly chosen timeframe (as a minimum requirement) also affects the medical use of the medicinal product to be registered.

In 2013, Müller reported the traditional use of nine species as well as that of honey for the treatment of wounds, burns, ulcers, and dermatoses. For *Lawsonia inermis* L. (Lythraceae); *Punica granatum* L. (Lythraceae); *Equisetum* sp. (Equisetaceae); *Commiphora myrrha* (Nees) Engl. (Burseraceae / listed as *Commiphora molmol*); *Nigella sativa* L. (Ranunculaceae); Trigonella foenum-graecum L. (Fabaceae s.str / Leguminosae); *Coriandrum sativum* L. (Apiaceae), *Myrtus communis* L. (Myrtaceae), and *Sanicula europaea* L. (Apiaceae)[1] he

[1] The taxonomic validation of the species is based on http://mpns.kew.org/mpns-portal/ and www.theplantlist.org and was done by the authors of this paper.

could establish evidence of a continuous traditional use over centuries up to the present day. For example, myrrh (*C. myrrha*) was first recorded for the treatment of wounds in the Papyrus Ebers 1550 BCE (cf. Müller, 2013, 176). Ancient Egyptian Papyri describe its use against burns, ulcers, and dermatoses as well. Around 450 BCE myrrh occurs in "The Histories" of Herodotus as a vulnerary; it was prominent among the wound treatment agents of the Middle Ages and kept this position continuously throughout all centuries (Müller, 2013, 170–197). For example, it is mentioned in pharmacological and surgical handbooks of the 1830s as useful for promoting granulation, treatment of ecoriated gingiva and so on. This has been confirmed in the famous "Lehrbuch der biologischen Heilmittel" by Gerhard Madaus a hundred years later (Madaus, 1938). Aside from stomatological indications in Europe, the use of myrrh was more and more abandoned, while a lively tradition of its use for wound treatment, in particular related to the diabetic foot syndrome, continued in Arabic countries (Müller, 2013, Alzahrani and Bakhtoma, 2010). This example shows the power of historical research as a proof of use well beyond the 30 year period and besides particular brands. These studies offer many examples how an extended time frame could offer opportunities for an approach which uses historical documents as a proof of use well beyond the 30 year period.

Another example are the traditional uses of *Crataegus* spp. and *Leonurus* sp. Schantz (2009) traced the medicinal use of *Crataegus* spp. back to the work of Dioscorides (c. 40–90 CE) and shows that there is a continuous tradition through the Middle Ages and Early Modern times up to nineteenth and twentieth centuries. Schantz includes 58 written sources covering uses of *Crataegus* spp. for the period 100 BCE up to 2005 and 44 for *Leonurus* sp. since the Middle Ages. Crataegus, for example, has not only been used for complaints of the heart, which is the predominant indication today, but against a variety of diseases like gastrointestinal disorders. Not all of these could be confirmed by recent bio-scientific or clinical studies and this would in fact not be required under the THMPD, where plausibility of a medical use needs to be demonstrated but not efficacy. The continuous use over two thousand years unveiled by a professional evaluation of historical sources provides a very profound basis for modern uses, which could be explored further. It also demonstrates a considerable degree of safety. The same is the case with *Leonurus* sp. which has a continuous tradition for cardiac indications from the Middle Ages.

With regards to proof of safety all material available (this applies to the past as well) needs to be assessed and evaluated as a matter of principle. The nephrotoxicity of the *Aristolochia* species, for instance (Michl et al., 2014), led to the infamous incident involving Belgian slimming preparations. However, this had been a known factor since 1815, if not even since antiquity, and has been described in unequivocal terms. (Scarborough, 2011).

5. Historical evidence as an essential requirement

For the authorization or registration of medicines, the European and German medicine laws stipulate two different procedures for providing evidence-based proof of efficacy and safety. In the registration process, on the one hand, evaluation respects the hierarchy of evidence, which, for instance, is also used by the Cochrane Collaboration (e.g. Cochrane GRADE: http://www.cochrane.de/de/%C3%BCber-grade). On the other hand, there are, as a criterion for the registration of traditional herbal medicines, these aspects of efficacy and safety, demonstrated on the basis of “traditional use” and, moreover, considered scientifically plausible. The regulatory authorities only take the law as their point of reference. However, we are undoubtedly dealing with scientifically evaluable data useful as evidence for the use of the medicine in question, the only difference being that, in this instance, in evaluating the methods a different scientific discipline (history) needs to be consulted. Evidence-based medicine is open to the various kinds of scientific insights, including those of epidemiology, medical sociology or the histories of pharmacy and medicine (Sackett et al., 1997; Eichler et al., 2015). For questions regarding the safety of use under practice conditions or the historical origin of a treatment, the relevant scientific methods can provide additional insights.

With the registration of Traditional Herbal Medicinal Products in particular, safety of use (innocuousness) is a key aspect when assessing the risk-benefit ratio. Therefore, particular value is placed on the exact scientific assessment of the data regarding “traditional” use, and on the insights that may be gained in this process with respect to modes of application, indications and possible side effects etc. If, therefore, “traditional use” is chosen as a basic criterion, as the law stipulates, it is in our view essential that *this traditional use is scientifically assessed and evaluated,* (Helmstädter and Staiger, 2014), even if at present the law does not explicitly ask for this. This would also meet one of the requirements set out by the WHO, which is “[to] identify sources of evidence, whether historical, traditional or scientific, which support or invalidate a particular therapy” (WHO Traditional Medicine Strategy 2014–2023)

6. Methodological recommendations for the proof of tradition

There are plenty of guidelines and recommendations relating to Section 39a of the German Medicinal Products Act in the publications of the EMA and of the national regulatory authorities. However, in a recommendation issued by the German Federal Institute for Drugs and Medical Devices (*Bundesinstituts für Arzneimittel und Medizinprodukte, BfArM*) one also finds the following statement, which highlights the concern expressed in this contribution, “A great diversity of documents are accepted as proof of tradition; applicants can use their own creativity in collating their documents!” (BfArM Arzneimittelzulassung). While ‘creativity’ may have a role to play in the arts, the humanities, including history, require methodical procedures (as do medicine and pharmacy which are both informed by the natural sciences) which emphasize criteria such as plausibility, comprehensibility, transparency and structure.

A critique of sources is a central aspect of history as a science. Any transmitted record can be a source for the historian, but whether or not it is useful depends on the question investigated. It is important to keep in mind that the selection of sources in itself constitutes an interpretation. This applies as much to the history of pharmacy, as it does to history in general.

The critical assessment of sources as the benchmark for historical evidence has been standard procedure in the history for more than 200 years (Gierl, 2012). It consists of several stages.

The first step is to establish external criteria: Is the source genuine? Is it the author's own work? Is it original? Is it based on the author's own observations or insights? How was the source transmitted (in its original or in a secondary form)? Is it a (reliable) translation? (Müller, 2013; Pommerening, 2006).

The importance of such assessment criteria for plant monographs which rely on more recent documents from the last thirty or forty years, has been demonstrated by John K. Crellin, who has given examples from North America. For example, the evidence from the various editions of standard pharmaceutical texts has been chosen arbitrarily. In some cases, only two citations from different years were considered sufficient as proof of continued use.

Often primary sources such as recipes or formulae are not sighted but cited through secondary sources. They are not properly assessed or scrutinized, an omission that can lead to mistakes and misinterpretations. The Herbal *Materia Medica* editions also reveal that sources which are not cited in the original may contain – often quite serious – mistranslations.

Bibliographies are often restricted to printed sources. Hand-written sources, such as the partly preserved pharmaceutical records

(*Rezeptkopierbücher*) from the mid-nineteenth century contain medicinal formulae, the patients' names, also medicinal formulae the name of the prescribing physician and the cost of the medicine dispensed, but are not taken into consideration. Such unprinted sources have so far not been drawn on to support the proof of tradition, even though they can provide continual and detailed evidence regarding the dispensing of a particular medicinal product over several centuries (Hoffmann, 2014, 94–105). Similarly, patients' records form surgeries or hospitals have not been considered (Dietrich-Daum et al., 2008).

The external verification of sources is followed by an internal one looking at the origin of a source: Who composed it, when, how, where and for what purpose? Are there indications as to the author's intentions? Has information been withheld? What is the source's historical context, including economic, social and legal aspects? Are there concepts, occurrences or personal information that remain ambiguous?

Consequently, for the proof of tradition individual elements of evidence need to be examined thoroughly in order to exclude idiosyncrasies. The authors of the citations also need to be scrutinized regarding their intentions. What time and place did the author live in? One also needs to understand who commissioned the source in question. The overall aim is to create a broad pattern of observation with the inclusion of primary sources (Crellin, 2008).

Once the sources have been verified one needs to ask how instructive and relevant a source is for the original research question, in this case, submitting proof of tradition for a registration procedure. Efficacy is proven by demonstrating its presence in concrete modalities of application, while safety is proven by demonstrating the absence of harmful effects, in other words, source criticism requires diverse approaches.

Importantly, can the data available, as a whole, yield sufficient evidence for the safety and medicinal use of the medicine submitted for registration? What kind of data is able to provide valid information? This depends, for instance, on the product type (at an early or later stage of a value chain) – plant, drug, extract – one is dealing with.

It also needs pharmaceutical expertise to establish whether, and to what extent, historical sources yield information on the plant parts and extraction methods used. Both have an important influence on the product's composition. In this case the traditional use of a plant without the inclusion of further details about its pharmaceutical preparations is less informative.

The resin of the olibanum or frankincense tree (*Boswellia serrata* L., Burseraceae) is a good example of an herbal medicine with well-documented traditional use. Frankincense has been used since antiquity in medical systems in and outside of Europe (Stueker, 2006). The indications documented include external applications, for instance, – in wound care or for inflammatory and rheumatic conditions – which mostly go back to Indian Ayurvedic medicine. These reports prompted extensive pharmacological studies which demonstrated the botanical drug's anti-inflammatory properties and led to the isolation of a specific active metabolite: the boswellic acids (Abdel-Tawab, 2011; Ammon, 2016). However, no commercial frankincense preparation has been on the market for more than thirty years in the European Union. Consequently, despite this uninterrupted tradition of use and the "plausible" effect demonstrated in pharmacological and clinical experiments, it has so far been impossible to register frankincense preparations in Germany.

The extended time period proposed here for the proof of tradition should not go back further than the time of the first publication, in 1735, of *Systema Naturae,* the multivolume standard work of the botanist Carl Linnaeus (1708–1778). His classification, which also uses binomial designations for plants, forms the foundation of today's biological nomenclature. At the same time, in order to avoid drawing false conclusions regarding medical uses one needs to keep an eye on the change of long-lived medical (body-) concepts (like the humoral pathology).

With traditional uses that continue into the present time and for which evidence needs to be supplied in the case of traditional herbal medicinal products, one needs to understand what exactly the proof of tradition relates to. Here, examinations are useful that make use of epidemiological methods as well as the scientific preparation of data arising from the medical and pharmaceutical practice. The relevant literature can supply a wealth of material on how these examinations need to be conducted to a very high standard. An important repository of what can be considered modern historical sources is the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/).

Pharmaceutical collections and standard reference works are an important source of information and can support a well-founded proof of tradition based on a broad selection of sources, but it is beyond the scope of this article to list them. Some of these sources are now available in digital format and can easily be accessed online (Mönnich, 2006). Studies from the history of pharmacy which contain chronological bibliographies can also be a good starting point (Müller, 2013; Schantz, 2009). On the whole, evaluation of the older literature needs expertise and competence which can usually be found among the representatives of both the history of medicine and the history of pharmacy. It is essential that they are consulted for the proof of tradition. There are initiatives in North America worth noting. John K. Crellin, for instance, is taking the regulatory authorities to task. In his opinion it is up to the authorities to make sure, when considering the registration of an herbal medicine, that its proof of tradition is based on evidence ("sound scholarship", Crellin, 2008). In this context the EU will need to develop a much sounder strategy. This is in the interest of the consumers and the manufacturers. In the future it will contribute to improving the quality of application and safety of use of herbal medicines.

7. Conclusion

Just like with other therapies, the therapeutic use and formal registration of Traditional Herbal Medicinal Products is largely based on their longstanding tradition. Many institutions – both at a national and European level – have contributed to this. For example, since 2004 the EMA committee for herbal medicinal products (HMPC) has made important contributions to implementing the THMP directive, also by assessing the scientific evidence for a large number of traditionally used medicinal products, and in issuing respective monographs, but here we argue that a more rigorous assessment of the historical data is nevertheless consequential. In order to ensure that this therapeutic use complies with the requirements of evidence-based medicine, it is essential that *all* relevant data, not only those stipulated in the regulatory provisions (30 years, product reference), are scientifically assessed and evaluated.

Clearly, from among the natural, life and cultural sciences, the scientific methods considered authoritative in each case, need to be used. The same is the case with historical aspects. Despite of restriction of the THR to the more recent past (i.e. the 30 years specified by the EU Directive), historical evidence is essential and needs to be based on sound scientific methods. Best practice is required to ensure that patients will benefit from the "best available evidence" that is the hallmark of evidence-based medicine.

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