Chemistry and the definition and isolation of 'active principles' of plants in the late 18th and early-19th centuries

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Abstract

Discussions of possible procedures to analyze materials originated in the various kingdoms of nature became increasingly more frequent in the second half of the 18th century. While in the wake of the work performed by Antoine Lavoisier and his group, the analysis of a considerable part of mineral compounds no longer posed a problem, the same was not the case of the substances of plant or animal origin. In this paper we discuss Pierre-J. Macquer's and Antoine –F. Fourcroy's ideas on the analysis of materials originated in the plant and animal kingdoms and how the results of such analyses were gradually included in pharmacopoeias in the early decades of the 19th century.

Keywords

History of Science; Chemical analysis; Medicinal principles; Pharmacopoeia; 18th century; 19th century

A química e a definição e o isolamento dos 'princípios ativos' vegetais entre final do século XVIII e início do XIX

Resumo

Na segunda metade do século XVIII tornaram-se cada vez mais frequentes os debates sobre as possíveis maneiras de analisar os materiais dos diferentes reinos da natureza. Se, com o trabalho de A. Lavoisier e seu grupo as análises de boa parte dos compostos do reino mineral deixaram de representar um problemas, o mesmo nao se observou com relação aos compostos dos demais reinos. Neste trabalho discutimos as ideias de P.-J. Macquer e A.-F. Fourcroy sobre as formas de proceder à análise dos materiais dos provenientes dos reinos vegetal e animal, e como os resultados dessas análises foram, pouco a pouco, incorporadas nas farmacopeias no início do século XIX.

Palavras-chave

Historia da Ciência; Análise química; Princípios medicamentosos; Farmacopeia; Século XVIII; Século XIX

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Introduction

Chemistry has a quite interesting story to tell relative to the period from the earliest studies of the medicinal virtues of plants to the 19th century, when such virtues were defined and named as active principles. This story involves major figures in the history of chemistry and the analytical studies they performed relative to the three kingdoms of nature, thus evidencing the huge difficulties posed by the study of living things, plants in particular as concerns our present purpose.

The number of plants used as medications was always large. In the 18th century, as a result of the countless travels of naturalists, that number grew exponentially, especially since the arrival of American plants in Europe. Under such circumstances it became increasingly difficult to control their provenance, which often was the single parameter available to distinguish between genuine products and adulterations. The solution to the problem posed by the identification of the new materials used as medicines, many of which came from the Americas, largely depended on the development of the pharmaceutical and chemical sciences and their search for more precise notions as to the composition of plant-derived medicines.

It is worth to remind that plants such as cinchona usually arrived in Europe without an accompanying description likely to grant a minimum of safety to prescriptions.[1] So for instance, by the end of the 18th century the physician Celestino Mutis (1732-1808) complained of the lack of information that allowed "recognizing in them [cinchona plants] their peculiar eminent virtues based on their most outstanding qualities"[2]. For that reason, also other doctors like him put their hope in that chemical studies would provide information on the composition of the parts of plants that allegedly held their medicinal virtues. This is to say, chemists were expected to elucidate the composition of the medicinal principles of plants, which at times even had specific

[1] For that reason and the fact that the cinchona plants that arrived in Europe came from different parts of the Americas, by the end of the 18th century the Spanish government organized expeditions specifically meant to gather information on them and other medicinal plants; see Antonio González Bueno, & Raúl Rodríguez Nozal, *Plantas americanas para la España Ilustrada: génesis, desarollo y ocaso de expediciones botânicas* (Madrid: Editorial Complutense, 2000).

[2] See, e.g., José Celestino Mutis, *El arcano de la quina* (Madrid: Ibarra, 1828), 87-9 [facsimile edition Madrid: Fundación de la Ciencia de la Salud, 1994). It is worth to note that while this book was published only after Mutis' death, its editor, the apothecary M.H. de Gregorio observed that Mutis had written it as early as in 1792.

names. For instance, the medicinal principles of Peruvian bark were often referred as 'febrifuge principle'[3].

The quest for the medicinal principles of plants – among many other so-called 'principles', such as the coloring and the odoriferous – raised an additional issue: did the principles exist as such in the plants, or were they formed during the preparation of the medicines or in the course of chemical analysis?

Macquer: difficulties impossible to overcome

Let us see how Pierre-Joseph Macquer (1718-1784), a reputed chemist in his time, approached this issue in his *Elements of the Theory and Practice of Chymistry*, published in the mid-1700s.[4] In the section headed "A General view of Chymical Decomposition" of volume 1, namely, the one devoted to the 'Elements of the Theory', Macquer explains that analysis separates the principles that compose plant, animal and mineral bodies in a definite order. As concerns the plants, Macquer first discusses the procedures that "extract from vegetables all the principles they will yield without the help of fire", followed by the "operations for decomposing plants by degrees of heat".[5] Gradual application of fire was the procedure most commonly used to separate those principles, being that the most volatiles ones separated first. However heat itself could induce new combinations of the principles in plants, or partially decompose them, which made it

[3] Term 'febrifuge principle' appears in several publications from the beginning of the 19th century in which mention is made of a memoir on the analysis of cinchona read by Armand Séguin (1767-1835) at *Institut National*; see, e.g., Anonymous, "Extrait d'un mémoire sur le principe febrifuge du quinquina, par le C. Seguin," *Bulletin des sciences par la Société Philomatique de Paris* 77 [1803]): 130-1; see also Sacha Tomic, "L'Analyse chimique des végétaux: le cas du quinquina," *Annals of Science* 58 (2001): 287-309, which gives details on Séguin's memoir, 293-4. According to the *Oxford English Dictionary*, the first mention of term 'febrifuge principle' in English is in a translation of Alexander von Humboldt's *Versuch über den politische Zustand des Königsreich Neu-Spanien*; see *Political Essay on the Kingdom of New Spain, transl. J. Black. (London:* Longman Hurst Rees Orme and Brown, 1811), vol. 2, 402; *OED Online*, Oxford University Press (Septermber 2015). http://www.oed.com.libproxy.ucl.ac.uk/view/Entry/168355?rskey=jsaoim&result=2 (accessed December 6 2015).

[4] Pierre-J. Macquer, *Elemens de chymie théorique* (Paris: P.-Fr. Didot, 1756) and *Elemens de chymie pratique* (Paris: P.-Fr. Didot, 1756); in the present study we quoted from an English translation: *Elements of the Theory and Practice of Chymistry* (London: A. Millar & J. Nourse, 1758).

[5] Ibid., I: 208.

difficult to establish which the original principles and their properties were.[6] As a result, much skill was required from anybody attempting to perform this type of analysis.

In the second volume of the work, devoted to the 'Elements of Practice', Macquer lists in full detail the procedures used to extract several 'substances' from plants. This is to say, the analyses to which plants were subjected to separate and identify their components. Such procedures could be applied as a set or individually according to the intended outcome. The first stage of analysis, i.e., the one without use of fire, was sometimes sufficient, for instance, when the aim was to separate some 'essential oils'. However, more drastic procedures were needed when one sought to perform a more 'intimate' type of analysis.[7] The following are the various types of analyses performed in Macquer's time.

The first and most simple procedure was 'expression', which allowed extracting the 'Essential Salt', 'Oils', 'Fat Oils', or 'Essential Oil' of plants, although it could be quite time-consuming.[8] Next Macquer describes 'Trituration', in which macerated plants were agitated in water over a long period of time to induce the separation of salts, oils, and 'earthy parts'.[9] However, these two methods did not systematically yielded an accurate analysis, because they merely separated the liquid parts of plants, which were "impregnated indeed with almost all the principles of plants, which however are still combined with each other, and barely separated from the grossest earthy and oily parts"[10]. More effective procedures were thus needed, now involving the use of fire. Therefore, the third type of analysis required "a degree of heat not exceeding that of boiling water" to perform procedures such as distillation, decoction in boiling water, distillation *per descensum*, and infusion. Those procedures allowed obtaining 'odoriferous liquors', 'essential oils' and 'fat oils' from plants.[11]

In the case of plants that did not yield 'fat oils' or 'essential oils', analysis should continue "by means of a graduated heat, from that of boiling water, to the strongest that can be applied to them in close vessels"[12]. Macquer admits the difficulty inherent to the application of this type of analysis to the identification of the characteristic parts of different plants:

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6 Ibid., I: 135.

7 Ibid., II: 106.

8 Ibid., II: 92-8.

9 Ibid., II: 99-106.

10 Ibid., II: 106.

11 Ibid., II: 125-44.

12 Ibid., II: 168-76, quotation in 168.

> "Most vegetable substances, when distilled with a Strong fire, yield the same principles with that which we have chosen for an instance. Entire plants of this kind, [...] all such matters being distilled yield a Phlegm, an Acid, a thin oil, air, and a thick Oil, and the products of their several analyses differ from each other, only on account of the different quantity or proportion that each contains of the principles here enumerated."[13]

The last procedure listed is combustion, which Macquer defines as "a kind of violent and rapid analysis made by fire, which separates, resolves, and decomposes several of its principles". That procedure is indicated when one seeks to extract a fixed caustic alkaline salt or a simple fixed salt from the plants. These materials were "the work of the fire", since they did not exist as such in the plants before being burned.[14] Thus Macquer writes:

> "The phenomena observed in the burning of a vegetable substance, and the production thereby of a Fixed Alkali, seem to prove that this Salt is the work of the fire; that it did not exist in the plant before it was burnt; that the plant only contained materials adapted to form this Salt; and that this Salt is no other than a combination of some of the Acid, united with a portion of Earth, by means of the igneous motion."[15]

To summarize, Macquer points to the difficulties associated with the identification of the principles in plants, including the medicinal ones, when it was attempted by means of chemical analysis. To overcome this problem he looked into the works by other authors, like Hermann Boerhaave (1668-1738), however, he found that the details given for the 'degree of the fire' or the duration of heating did not suffice to reproduce the published results.[16] Thus he was not able to overcome the difficulties posed by the analysis of plants so as to isolate the principles that accounted for some of their medicinal 'virtues'.

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[13] Ibid., II: 175.
[14] Ibid., II: 179-81.
[15] Ibid., II: 181.
[16] Ibid., II: 182-6.

Plant principles and the 'New Chemistry'

As chemical analysis was at the very core of the emergence of the so-called 'New Chemistry', it is worth to mention briefly the work by Antoine Lavoisier (1743-1794) and his book, *Elements of Chemistry*.[17] According to him the composition of minerals did not seem to pose any problem, since the chemical elements were operationally defined as the end result of analysis. Thus it had become possible to identify and name most of the materials from the mineral kingdom.[18]

However, upon approaching plants, Lavoisier realized that analysis posed countless difficulties. To begin with plants contained "neither water, nor [empyreumatic] oil or carbonic acid", which were usually obtained by means of dry distillation (also known as naked flame distillation at that time).[19] Lavoisier believed that those substances were formed in the course of the procedure due to the "action of twofold or threefold affinities" (i.e., combination of two or more of the substances present in plants) which were more complex in the plants that contained nitrogen and phosphorus,[20] and even much more in "animal matter".[21]

In Lavoisier's view "the true constitutive principles of the plants are only three […] to wit, hydrogen, coal [carbon], and oxygen"[22]. In addition, chemical analysis of specimens from the main classes of plants yielded very similar results. To be sure, analysis in the terms of carbon, hydrogen and oxygen contributed almost nothing to the studies and practice of the users of plants for therapeutic purposes, who were thoroughly acquainted with the differences among species (which looked the same to the untrained eye). Neither the knowledge of the products of distillation was useful, as according to Lavoisier they were not present as such in plants and thus did not serve as markers for them.[23] Shortly, the chemical identification of the parts of plants associated with their medicinal virtues remained a problem for a while, demanding contributions from other men of science.

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[17] Antoine-L. Lavoisier, *Traité Élémentaire de Chimie, présenté dans un ordre nouveau, et d'après des découvertes modernes* (Paris: Cuchet, 1789). In the present study we quoted from the English translation by R. Kerr, *Elements of Chemistry in New Systematic Order, Containing All Modern Discoveries* (Edinburgh: William Creech, 1790).
[18] Ibid., xxix.
[19] Ibid., 124.
[20] Ibid., 124-5.
[21] Ibid., 127.
[22] Ibid., 123.
[23] Ibid., 125-6.

Fourcroy's 'Vegetable Chemistry'

Thus Antoine-François de Fourcroy (1755-1809) sought for new paths to solve the quandary posed by the chemical analysis of plants in his *System of Chemical Knowledge and Its Applications to the Phenomena of Nature and Art,* published at the very beginning of the 19th century.[24] While admitting that the explanations he suggested were not definitive, he was hopeful the problem could be solved in the near future. His 'temporary' solution had to do with one of the branches of chemistry that he named 'vegetable chemistry' and that he optimistically characterized as follows:

> "Vegetable Chemistry treats of the analysis of plants and their products. A short time ago, it consisted only of a series of the processes of those arts which extract, purify, and appropriate to four wants, the different materials of vegetables, or prepare them in different ways for the relief of our infirmities. At present its object is more extensive, its subject more enlarged, and its views in some degree more elevated. It possesses new methods of decomposing the products of plants, and of ascertaining the order of their compositions: it begins by explaining their intimate nature, their formation and connection; [...] it will ultimately succeed in explaining the laws of vegetable economy […] It exhibits the manner in which mineral substances [chemical elements] unite in triple compounds to form vegetable substances".[25]

Fourcroy attempted to solve the problem by calling the materials resulting from the decomposition of organized bodies 'products' of analysis rather than 'principles'.[26] In this regard, he stated that one could distinguish "four types of analyses: mechanical analysis, spontaneous or natural analysis, analysis through fire, and analysis through reagents"[27]. The crux of the matter was to focus on the "differences among the analyses based on their results [products]", which once again resulted in four types of analyses: "immediate or proximate analysis, mediate or remote analysis, simple or true analysis,

[24] Antoine-F. Fourcroy, *Système des connaissances chimiques et de leurs applications aux phénomènes de la nature et de l'art* (Paris: Badouin, 1800-1). In the present study we quoted from an English translation: *A General System of Chemical Knowledge: And Its Application to the Phenomena of Nature and Arts* (London: Cadell et al., 1804).

[25] Ibid., "Section First", I:, 8-9.

[26] Ibid., I: 78.

[27] Ibid., I: 78-80; quotation is on 80.

and complicated or false analysis."[28] Let us look more closely into this matter. Fourcroy says:

> "I call that the mechanical analysis which, by mechanical means, such as pounding, washing, or pressure, affords the less complicated matters contained and mixed in more compounded bodies. It is only a kind of dissection, a commencement of analysis, rather than a true chemical analysis."[29]

Thus the various compounds that formed plants, starch and mucilage in particular, were isolated and could be analyzed separately.

The compounds resulting from immediate analysis were next subjected to mediate or remote analysis to discover their 'intimate composition'. Although the last two types of analyses were related, they were opposite one to the other:

> "The simple or true analysis [...] gives the products without alteration, such as they existed in the compound which afforded them. The character by which this kind of analysis is distinguished, is that the products it affords being re-united, form again the compound such as it was in its nature and quantity before decomposition."[30]

Contrariwise, false analysis, which was performed through the application of fire, e.g., to plant and animal materials, yielded altered products.[31]

Therefore, it seems quite clear that according to Fourcroy, 'true analysis' was the most relevant one in the quest for the 'compounds' associated with the medicinal action of plants. 'True analysis' could contribute to the understanding of how medicines acted on the organism (or on the 'animal economy', to employ a contemporary expression) and thus fulfill what Fourcroy held to be the 'highest call' of animal chemistry.[32]

[28] Ibid., I: 80.
[29] Ibid., I: 78.
[30] Ibid., I: 82.
[31] Ibid., I: 83.
[32] Ibid., I: 9-10.

Final remarks

Pointing to a path, however, did not mean to have found the intended solution, as simple or true analysis was seldom attained. Nevertheless, Fourcroy believed in the rapid development of 'pharmacological chemistry', one of which goals was the "analysis of simple medicines" so as to isolate their medicinal principles.[33]

Indeed, it did not take too long before peculiar substances considered to be active principles were isolated from plant matter. Such event was initially attended by a heated debate on whether such substances truly accounted for the healing properties of plants, as well as on whether they were an original component of the plants, or rather were a product of analysis.[34]

In any case, the results of chemical analysis were gradually included in pharmacopoeias. For instance, when Louis-Antoine Planche (1776-1840) translated *Farmacopea generale ad uso degli speziali e medici moderni* into French in 1811, he added long notes describing the results of the chemical analysis of many of the included medicines.[35] In this way, Planche was fulfilling the goals set by the author of *Farmacopea generale*, the Paduan doctor Luigi Vincenzo Brugnatelli (1761-1818), who in 1802 had stated that doctors should know "in which of these principles resides the active principle of the drugs [used in] Medicine"[36]. Brugnatelli was seemingly so pleased with Planche's translation, that on that very year (1811) he published a *Materia medica vegetabile ed animale* as a complement to his earlier work, in which he provided a much larger amount of data on the analysis of plant and animal 'substances'. In that book the medicines are presented in alphabetical order, and each item further includes the botanical description of the plants, their medicinal virtues, pharmaceutical preparation and dosage forms.[37]

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[33] Ibid.

[34] For the case of some Brazilian plants, see Márcia H.M. Ferraz, Ana M. Alfonso-Goldfarb, & Silvia Waisse, "A Formação da Matéria Médica Moderna a partir do Século XIX: O Brasil como Estudo de Caso," *Estudos do Século XX* 12 (2002): 179-96.

[35] Luigi V. Brugnatelli, *Farmacopea generale ad uso degli speziali e de' medici moderni, ossia, Dizionario delle preparazioni farmaceutico-mediche semplici e composte più usitate ai nostri tempi e conformi alle nuove teorie chimico-mediche* (Pavia: Giovanni Capelli, 1807); Luigi V. Brugnatelli, *Pharmacopée générale a l'usage des pharmaciens et des médecins modernes* (Paris: Colas, 1811).

[36] Luigi V. Brugnatelli, *Farmacopea ad uso degli speziali e medici moderni della Repubblica Italiana, aggiuntovi la tavola della sinonimia delle moderne nomenclature chimiche e la tariffa delle preparazioni in questa farmacopea riportate* (Pavia: Giovanni Capelli, 1802), 40

[37] Luigi V. Brugnatelli, *Materia medica vegetabili ed animale, ossia, Dizionario compendioso della storia naturale, chimica e medica delle piante e sostenze vegetabili e animali più opportune a conoscersi dai medici moderni : per servire di compimento alla Farmacopea generale pubblicata in Pavia nel 1807 ed in Parigi nel 1811* (Pavia: Bolzani, 1811).

Those developments notwithstanding, the active principles isolated from plants and animals only entered the pharmacopoeias several decades later, to wit, after their number had much grown and they were recognized as responsible for the healing action of such substances.