

THE “FEBRIFUGE PRINCIPLE” OF CINCHONA BARKS

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ABSTRACT

The antipyretic properties of cinchona barks were known since ancient times in South America, particularly in Peru. The use of these barks in medicines against “fevers” in Europe in the 17th century made the exploitation of cinchonas of Peru a highly productive process, and those cinchona trees became menaced. The Portuguese government aware of the problem searched an alternative in cinchona varieties existing in Brazil. By the beginning of 19th century, samples of different Brazilian barks were shipped to Portugal in order to evaluate their therapeutic properties, in particular their antipyretic properties. Clinical and chemical studies were carried out in Coimbra and Lisbon, by the most eminent scientists of that time, in order to find out the best way to use the barks and identify the “febrifuge principle”.

During this research, Bernardino António Gomes isolated in 1810 the first known alkaloid – the cinchonine.

This discovery raised international interest and led in 1820 to the isolation of quinine, by Caventou and Pelletier in France.

This reinforced the interest in cinchona barks and the producing countries tried to establish a monopoly, forbidding the export of seeds and plants. Some European governments studied then possible solutions for the problem, namely acclimatizing cinchonas in their African and Asian colonies. Getting the plants was difficult, but finally, in Dutch and British colonies, large plantations of cinchonas were made, and so the import from South America was no longer needed. The Portuguese also tried to develop plantations in different regions in Africa. In São Tomé the culture of the cinchonas was economically sustainable and a small pharmaceutical industry was developed during some decades.

In this communication we present a brief account of the isolation of cinchonine and of the development of the culture of cinchona trees in Portuguese colonies.

1. Introduction

Since long times Humanity has suffered very serious health problems due to malaria. The antipyretic properties of cinchona barks were known since ancient times in South America, particularly in Peru, from where cinchona trees originate. However, only in the 17th century, in Europe, with the discovery of the therapeutic properties of cinchona barks, a more effective treatment for this disease could be envisaged. The use of these barks in medicines against “fevers” in Europe in the 17th century made the exploration of cinchonas of Peru a highly productive process, and cinchona trees became menaced. By the end of the 18th

century, bad management of natural resources, together with immense greed, almost turned these trees in endangered species.

Portuguese government, aware of the problem, searched an alternative to Peruvian barks¹ in cinchona varieties existing in Brazil. By the beginning of 19th century, samples of different Brazilian barks were shipped to Portugal in order to evaluate their therapeutic properties, particularly their antipyretic action.

It was also intended to find out the most efficient way for the administration of medicines obtained from the barks, as well as to identify their “febrifuge principle”. In Lisbon and in Coimbra clinical and chemical tests were carried out, often in difficult conditions. The researchers faced some lack of material resources, as well as of scientific information, due to the political situation in Portugal. There are documents of this period that mention the destruction of reports related to those essays, in the consequence of French invasions², by the beginning of the 19th century³. However, the reports that survived all odds show the commitment of Portuguese scientists, namely Bernardino António Gomes in Lisbon and Thomé Rodrigues Sobral in Coimbra, in the study of those precious barks⁴.

During this research, Bernardino António Gomes isolated in 1810 the first known cinchona alkaloid – the *cinchonine*.

¹ It was intended to “(...) *tirar da referida casca amarga todo o partido e vantagem que da sua introdução, como hum succedaneo da casca do Peru, resultariao ao Estado, e á humanidade. A Nação he tributaria aos Hespanhoes de sommas incalculáveis pelo commércio passivo da quina peruviana*” [(...) *to extract from the bitter bark mentioned all the advantages , for the State and for the humanity, of its introduction, as a succedaneum of the Peruvian bark. The Nation pays to Spain very large amounts for the trade of Peruvian cinchona*] (Sobral, 1813, p.106).

² “*Desde a mesma invasão multiplicarão-se os pântanos, pela diminuição que soffreo a agricultura (...)*”, tendo-se verificado um aumento dos surtos de malária nestas regiões [“*Since the (French) invasion the swamps multiplied, due to the decrease that agriculture suffered (...)*”, an increase of the outbreaks of malaria in these regions was verified] (Leitão, 1813, p.25).

³ “*Havendo apresentado o Vice-Reitor da Universidade de Coimbra a impossibilidade em que se-acha o Lente d’aquella Universidade Thomé Rodrigues Sobral de poder concluir a Análise chimica da Quina do Brazil, cujos trabalhos estão tão adiantados, assim pelas circunstancias que occorrem a respeito do dito Lente, como de se-lhe-haverem queimado todos os papeis relativos a este objecto*”. [“ *The Vice-Rector of the University of Coimbra, having presented the impossibility for the Lente of that University Thomé Rodrigues Sobral to conclude the Chemical Analysis of the Brazilian cinchona, that was very much in advance, due to different circumstances, as all the papers related to this object were burnt* ”] (Castilho, 1814, p.227).

⁴ “(...) *he necessária uma paixão innata, uma paixão de génio, para que este Homem Illustre [Thomé Rodrigues Sobral] dedique ainda hoje á sciência que professa [referindo-se à análise química das cascas de quina] todas as suas forças e todos os seus desvellos!*” [“(...) *an innate passion, a passion of a genius is needed so that this Illustrious Man (Thomé Rodrigues Sobral) still dedicates to the science he practices (the chemical analysis of the barks) all his forces and all his care!*”] (Castilho, 1814, p.285).

In 1820 Pelletier and Caventou isolated quinine. These pharmacists not only confirmed the validity of the method used by Gomes to obtain cinchonine, but also recognized the valuable contribution of the Portuguese doctor to the later isolation of the most important cinchona alkaloid – the quinine.

These studies reinforced the interest in cinchona barks and their demand increased significantly. By the second half of the 18th century the export of barks became a very profitable business for the producing countries in South America, and these countries tried to establish a monopoly, forbidding the export of seeds and plants. At the same time, the avidity of the *cascarilleros*⁵ led to an unrestrained exploitation of the cinchona region⁶, threatening the regular supply of barks. In view of this situation, some European governments studied then possible solutions for the problem, namely acclimatizing cinchonas in their African and Asian colonies. Getting the plants to initiate this process was extremely difficult, given the policy of South American countries towards the export of plants and seeds. It was necessary to use some subterfuges⁷ to obtain the desired samples. Moreover, the conditions of shipment did not favor the preservation of the material obtained (Gomes, 1864). It was also necessary to overcome the difficulties related to acclimatizing the plants in a foreign habitat. The work carried out together by several countries, and many years of research and of frustrated attempts were on the basis of the implementation of this culture in European colonies. Finally, in Dutch and British colonies, large plantations of cinchonas were made, and since 1866 the large Dutch plantations, as well as the alkaloid content of the species grown there made unnecessary the import of barks from South America⁸.

2. The cultivation of cinchona trees in Portuguese colonies

⁵ Designation given to persons who worked in the extraction of the barks. (Costa, 1944).

⁶ The cut of the trees and the extraction of the barks were made in such a way that in given regions the extinction of this culture was feared (Landeiro, 1936).

⁷ The subornation of the *cascarilleros* was common practice (Gomes, 1864).

⁸ The Dutch plantations in Java became the main producers of cinchona barks from 1866 (Landeiro, 1936).

Around 1864 the plantation of cinchona trees was also attempted in Portuguese colonies⁹. This initiative was enthusiastically supported by Dr. Bernardino António Gomes (son), and later by his own son, Bernardino de Barros Gomes¹⁰. This way, and taking into account the tradition of the Gomes's family in the study of cinchonas, there was no objection to the development of this project.

Dr. Júlio Henriques¹¹ who promoted this initiative, supervised, in the Botanical Garden of the University of Coimbra, the preparation of the plants that later were sent to the Portuguese colonies, and also to Algarve, Azores and Madeira. Unfortunately, this first attempt had not a great success, due the poor quality of the seeds used. Only by 1868 a promising sample of seeds could be obtained, which later on was sent overseas¹².

The analysis of some publications of that time shows that the work of Júlio Henriques and his collaborators had no support in the colonies. Apparently the distribution of the plants arriving from Portugal was not carefully carried out and the motivation and training of potential producers was not undertaken. In one of the publications we can read: *“From the plants that came from Lisbon on the 4th October 1869, only ten survived; not many more were distributed! (...) Those that were shipped from Lisbon on the 4th March 1871, and that arrived here in April, only in November were distributed!”* In the same paper we also read the following: *“All this proves that the government should not only send the plants and seeds, but also have here people who can take care of them.”* (Ribeiro, 1875, p.71).

To help solving these problems, Júlio Henriques presented several suggestions, which included the raising of plant nurseries and acclimatization gardens, funded by the central government, as well as incentives, like *“(…) prizes in money to the farmers who took more and better care of the plants they received from the nurseries”*(Henriques, in Landeiro, 1936,

⁹ Dr. Welwitsch, well known naturalist of that time, advised the minister of Navy, Mendes Leal, to initiate the culture of cinchonas in the overseas Portuguese possessions. (Costa, 1940).

¹⁰ Bernardino de Barros Gomes published the book *Cultura das plantas que dão a quina*. His objective was the divulgation of relevant information about the work of English and Dutch scientists in this area. In this book one can also find an analysis of the geographic and climatic conditions of the Portuguese colonies where the culture of cinchonas could be successful (Costa, 1940).

¹¹ Professor of Botanic of the University of Coimbra and director of the Botanical Garden (Costa, 1940).

¹² In parallel to this work Júlio Henriques reunited large information, aiming at informing and supporting the farmers involved in this Project (Teixeira, 1946).

p.75) . However, in spite of all the work developed, only in São Tomé the culture of cinchona trees had significant results.

Initially in São Tomé the farmers preferred to invest in the more profitable culture of coffee¹³. However, since 1879, the economic crisis , which affected the coffee market, draw the attention of the farmers to the possibility of the plantation of cinchonas and within a few years all the higher altitude part of the island was covered with these trees.

After 1880, the dimension of the plantations led to the development of an industry of quinine salts in Portugal, what excited national pride. Even before this project was made real, the news already mentioned the use of the “(...) *large plantations of cinchonas in São Tomé (...)*” *in the production of quinine sulfate, as a way to “(...) oppose to the Haward one or to others (...)*”¹⁴ (Rosa, 1890, p.48). This situation was also considered an opportunity to demonstrate to other countries, in particular England, the value of Portuguese industry. Incidentally, in publications of that time, expressions that reveal a certain national animosity towards England are often found¹⁵. This situation seems to be caused by the English Ultimatum of 11 January 1890 that impeded Portuguese to expand their colonial empire between Angola and Mozambique¹⁶, fact which produced a large turmoil in the national political life.

In this context José Júlio Rodrigues¹⁷ (Professor in the Escola Politécnica of Lisboa) together with some producers and also the pharmacist João António Rosa funded the Sociedade Luso-Africana¹⁸ for the production of quinine salts. Later, after the extinction of

¹³ The farmers preferred to invest in the well known and profitable culture of coffee (Henriques citado em Landeiro, 1936, p. 75).

¹⁴ By that time, almost all the quinine sulfate used in Portugal came from England (Carvalho, 1890).

¹⁵ “ (...) *oxalá que o nacional [referindo-se ao sulfato de quinina português] que em breve teremos, consiga deslocar aquelle do mercado [sulfato de quinina inglês] porque é assim, que principalmente, devemos guerrear a orgulhosa Inglaterra (...)*” [“(...) *hopefully the national (quinine sulfate) that we will soon have, will displace that one in the market (English quinine sulfate) because this is the way that we should use to fight the proud England (...)*”] (Carvalho, 1890, p.80).

¹⁶ O *princípio do direito histórico* que assegurava a Portugal, como descobridor, a posse desses territórios foi substituído pelo *princípio da ocupação efectiva*. Desta forma, os ingleses expandiram o seu império numa região que pertencia, originalmente, a Portugal [The *principle of historic right* that assured to Portugal, as discoverer, the possession of a territory, was substituted by the *principle of the effective occupation*. This way the English expanded their empire in a region that belonged originally to Portugal] (Capelo et al, 1996).

¹⁷ Professor in the Polytechnic School of Lisbon (Costa, 1940).

¹⁸ The facilities of the plant were located in Lisbon, in the Estrada do Lumiar (Costa, 1940).

this society¹⁹, quinine salts were produced in the Laboratório Químico-Farmacêutico of Ribeiro da Costa²⁰.

In this period, when the strong competition of Java was not yet significantly felt, the quinine sulfate produced by the Portuguese industry²¹ was used in the continent and in the colonies and also in Brazil. However, the lack of technical and scientific orientation in the culture of the cinchonas led to a progressive impoverishment of the barks. The acquisition of richer raw materials, from the Dutch plantations was not economically profitable for Portugal. On the other hand, the great increase in the coffee and cacao prices led the farmers in São Tomé to substitute the cinchonas by cacao trees. Only the cinchonas existing in places which altitude did not allow other kinds of plantation survived to these changes (Costa, 1940). As a consequence of this situation, the Portuguese industry of quinine salts declined gradually²².

3. Final note

Around 1930, the successive crisis in the world market of quinine salts, as well as the lack of production, renewed the interest for the cinchona plantations in Portuguese colonies. The evaluation in terms of contents of present alkaloids was carried out and several possibilities for the re-launching of chemical industry in this area were studied. In spite of having a low content in quinine, São Tomé's barks were considered as good "*pharmacological barks*", what means that they could be used successfully for the preparation of different pharmaceutical compositions in which the action of all the cinchona alkaloids could be made good use. In this context, the idea of the production of *totaquina*, as a way of integrally profiting of the barks, started to grow. This way, at the same time that a low cost, but effective medicine could be obtained, a certain independence from the external market would be conquered.

¹⁹ The dissolution of the "Sociedade Luso-Africana" seems to be related to the death of some of the partners (Costa, 1940).

²⁰ Located in Lisbon, in Poço do Bispo (Costa, 1940).

²¹ The quinine sulfate was considered of good quality by the "Comissão de Química da Sociedade Farmacêutica Lusitana". According to the judgment of those analysts, it was "(...) a commercially pure product, not inferior to many of foreign origin (...)" (Alves, 1893, p.91).

²² The Portuguese industry of quinine salts was extinguished around 1918 (Teixeira, 1946).

Trying to avoid the errors committed in the past, the implementation of the facilities of the factory in the island was suggested. That way the expenses corresponding to the transportation of the raw material, and that had a strong impact in the final cost of the product, could be avoided. The strengthening of the economy of São Tomé, was another important consequence.

These plans included also a scientific supervising and specialized orientation for the culture of the cinchonas. The intention was to improve gradually the quality of the barks and at a longer term, to re-launch the Portuguese industry of quinine salts. (Landeiro, 1936).

Some references to a possible cooperation between the School of Pharmacy of the University of Coimbra and farmers in São Tomé, during the thirties of the 20th century, were found²³. However it seems that the dream of reviving the Portuguese industry of quinine salts did not take shape.

Personal contacts in São Tomé did not give any significant results, as after the independence in 1975, it is difficult to have access to documentation, great part of which was lost.

After a period of a certain commitment and enthusiasm in the implementation of the culture of cinchonas in Portuguese territories, a time of lack of interest followed, and this issue finally was forgotten. According to Costa, “*Surely, only in the Faculties of Medicine and Pharmacy this chapter of our history is mentioned and even then as an obligation (...)*” (1940, p.346).

However, it is important to refer that, independent from economic interests that frequently seemed to overcome the humanitarian side of the problem, Portuguese scientists always showed the greatest care and affection towards this project. Among them, the names of Joaquim dos Santos e Silva, Aloísio Fernandes Costa e Cardoso do Vale, deserve a special mention.

²³ “*A pedido da Direcção deste estabelecimento de ensino [referindo-se à Escola de Farmácia da Universidade de Coimbra] foram solicitadas amostras de quinas a todos os roceiros de S. Tomé. (...) A análise deste material, primórdio de estudos de maior envergadura a realizar, se interesse for revelado, está a ser ultimada no Laboratório de Farmacognosia. Os resultados, a publicar em breve, poderão servir de base à renovação consciente do que ainda resta das que foram razoáveis plantações de quinas*” [“*Following the request of the Direction of this teaching institution (School of Pharmacy of the University of Coimbra) samples of cinchonas were asked to all the farmers of São Tomé. (...) The analysis of these materials, precursors of studies of greater scope, that will be carried out if interest is shown, is currently undertaken in the Laboratory of Pharmacognosia. The results to be published soon, may be a basis to the conscious renovation of what still exists of the past cinchona plantations*”](Costa, 1940, p.347).

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