

## Pharmacy, quina and quinine in Portugal, 18<sup>th</sup>-20<sup>th</sup> centuries

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### Abstract

Quina and quinine played a considerable role in European pharmacy and medicine, becoming a relevant object of botanical, chemical and therapeutic studies, in addition to their commercial and industrial interest. In the present paper we analyze the introduction of quina and quinine into the scientific literature, 18<sup>th</sup>- and 19<sup>th</sup>-century pharmacopoeias in particular. We begin by a study case on the use of quina at Teaching Hospital of University the Coimbra at the turn of the 19<sup>th</sup> century. Next we discuss the isolation of cinchonine in Portugal and the polemics to which it gave rise among scientists from Coimbra and Lisbon (1810-1812), as well as several of the most relevant studies of quina and quinine conducted in Portugal at the turn of the 20<sup>th</sup> centuries. Finally, we approach the problems posed by the cultivation of cinchona plants and quinine extraction in the former Portuguese colonies, particularly the errors that led to the end of the quinine extraction industry in Portugal.

### Keywords

Quina; Quinine; Portugal; 18<sup>th</sup> century; 19<sup>th</sup> century; Pharmacy

### Farmácia, quina e quinina em Portugal, séculos XVIII a XX

### Resumo

A quina e o quinino tiveram papel muito importante na farmácia e na medicina europeias e tornaram-se objeto muito interessante de estudos botânicos, químicos e terapêuticos. Por razões económicas tornou-se, também, um objeto muito interessante de interesses comerciais e industrias. O artigo analisa a recepção da quina e do quinino em literatura científica em particular farmacopeias dos séculos XVIII e XIX. Os autores dão a conhecer os resultados de um estudo de caso realizado sobre a utilização da quina no Hospital Escolar da Universidade de Coimbra entre finais do século XVIII e o início do século XIX. De seguida os autores abordam a inovação portuguesa da descoberta da cinchonina, a polémica havida entre cientistas de Coimbra e de Lisboa sobre o isolamento da cinchonina (1810-1812) e analisam alguns dos estudos científicos mais relevantes sobre a quina e o quinino em Portugal entre finais do século XIX e a primeira metade do século XX. Na parte final o artigo incide sobre a problemática da cultura das quineiras nas antigas colónias portuguesas, a indústria da extração do quinino e os equívocos gerados e que ocasionaram a ruína da indústria de extração de quinino em Portugal.

### Palavras-chave

Quina; Quinina; Portugal; século 18; século 19; Farmácia

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## Introduction

Among the American drugs introduced in European therapeutics during the 17<sup>th</sup> and 18<sup>th</sup> centuries, quina (a.k.a. Peruvian bark, taken from *Cinchona* L.) was the most relevant.<sup>1</sup> Quina is the most representative of those drugs, not only due to its impact on therapeutics, but also to the various scientific works that had it as subject, namely, botanic works, and the market networks to which it gave rise.<sup>2</sup>

In addition to quina, also other American drugs, such as ipecacuanha (*Carapichea ipecacuanha* (Brot.) L. Anderson), guaiac (*Guaiacum officinale* L.), sarsaparilla (*Smilax* spp. L.), etc., were highly relevant, although with less impact and significance on science and European therapeutics.<sup>3</sup> We do not intend to discuss here the discovery of quina by Europeans or its reception in Europe; on this subject much has already been written and telling many different versions. Quina was first described as a febrifuge in 1638 by Antonio de la Calancha (1584-1654) and more detailed studies were performed on this medicinal property in the following years, in particular, the ones by Gaspar Caldera de Heredia (b. 1593) in 1663. From the same period we may mention Gaspar Bravo de Sobremonte (1603-1683) and Pedro Miguel de Heredia (1579-1655) who also left us testimonies about the febrifuge properties of quina published in 1661 and 1673, respectively.<sup>4</sup>

Independently from the history of its origin, arrival to Europe and the role Jesuits and the Pope played in its initial marketing, it is certain that quina filled an important therapeutic gap in European medicine. Its properties to combat fever and malaria were recognized and thus it enriched the European therapeutic arsenal.<sup>5</sup> The innovations that quina introduced, for example, in botany, pharmacy, medicine and commerce, were also felt in Portugal. In the present study we address some of the most important aspects of the introduction and consolidation of quina in Portuguese science, pharmacy and medicine by means of some case studies.<sup>6</sup> We first focus on its introduction into the scientific literature, pharmacopoeias in particular, before the discovery of cinchonine; then we discuss its use in the hospital setting, taking the Teaching Hospital of University

<sup>1</sup> See Francisco Guerra, *Historia de la medicina* (Madrid: Ediciones Norma, 1988), vol. 1, 383; Alfredo R. Marques de Oliveira, & Daiane Szczerbowski, "Quinina: 470 Anos de História, Controvérsias e Desenvolvimento," *Química Nova* 32, no. 7 (2009): 1971-4.

<sup>2</sup> See F. Javier Puerto Sarmiento, & Benito del Castillo, "Presentation," in Hipólito Ruiz, *Compendio histórico-médico comercial de las quinas* (Burgos: Caja de Ahorros Municipal de Burgos, 1992), 7-9.

<sup>3</sup> See Francisco J. Puerto Sarmiento, *El mito de Panacea: Compendio de historia de la terapéutica y de la farmacia* (Madrid: Ediciones Doce Calles, 1997), 336.

<sup>4</sup> See Guerra, I: 383.

<sup>5</sup> Ibid.; José L. Valverde, & José A. Pérez Romero, *Drogas americanas en fuentes de escritores franciscanos y dominicos* (Granada: Universidad de Granada, 1988), 183.

<sup>6</sup> See João Rui Pita, "A Quina e Outras Drogas Americanas na Produção Medicamentosa do Hospital da Universidade de Coimbra nos Finais do Século XVIII," *Mare Liberum: Revista de História dos Mares* 17 (1999): 197-228.

of Coimbra as case study; in the third part we discuss the influence of quina on Portuguese scientific activity - the discovery of cinchonine; in the fourth part we focus on the introduction of cinchonine and quinine into the Portuguese literature; the fifth part deals with the industrial exploitation of quina and the quinine extractive industry in Portugal. We present some results and some tracks of an ongoing research project about quina and quinine in Portugal between the late 18<sup>th</sup> century and the first half of the 20<sup>th</sup> century.

### Quina in the scientific literature: pharmacopoeias and reference books

Quina was included in the Portuguese pharmacopoeias quite early. The first Portuguese pharmacopoeia, i.e., *Pharmacopea Lusitana* (1704) by Caetano de Santo António (d. c.1730) did not include a monograph of quina, but described formulations that contained it.<sup>7</sup> Between 1704 and 1794 several non-official pharmacopoeias were published in Portugal.<sup>8</sup> The first official Portuguese pharmacopoeia, *Pharmacopea Geral* (1794) by Francisco Tavares (1750-1812) included formulations with quina. *Pharmacopea Geral* describes 24 American drugs, among them quina and *quina vermelha* (red quina), a distinction commonly made at that time. To the author of *Pharmacopeia Geral* red quina had some advantages over the common quina relative to the preparation of alcoholic formulations. In Tavares' opinion red quina, which existed also in Brazil, "contains more resin than the vulgar quina, which has more gum extract. For that reason red quina is better for preparations made with wines or alcohol, and the vulgar or yellow [quina] for the ones made with water"<sup>9</sup>. Some among other widely used American drugs: *abútua* (*Chondrodendron platyphyllum* (A.St.-Hil.) Miers); sugar, *almecega do Brasil* (*Protium heptaphyllum* (Aubl.) Marchand), Copaiba balsam (*Copaifera* spp. L.), balsam of Peru (*Myroxylon balsamum* (L.) Harms), cocoa, *cascailha* (*Croton eluteria* (L.) W.Wright), *cipó* (*Aristolochia esperanzae* Kuntze), *contra-erva* (*Dorstenia brasiliensis* Lam.), *erva-santa* (a.k.a. whitebrush, *Aloysia gratissima* (Gillies & Hook.) Tronc., *spigelia* (*Spigelia anthelmia* L.), guaiac, white ipecacuanha, jalap, *mamona* (a.k.a. castor oil plant, *Ricinus communis* L.), *pechurim* (*Laurus pechurim* L.), *quassia* (*Quassia* spp. L.), sarsaparilla, *sassafrás* (*Sassafras* spp. J.Presl.), *Serpentaria virginiana* (currently, *Aristolochia pistolochia* L.), *sénega* (a.k.a. senega snakeroot, *Polygala senega* L.) and *simaruba* (*Simarouba amara* Aubl.).<sup>10</sup>

<sup>7</sup> See João Rui Pita "A *Pharmacopea Lusitana* de D. Caetano de Santo António ou Quando Se Faz 'Divino' o Remédio Humano," in *Pharmacopea Lusitana*, ed. João Rui Pita (Coimbra: MinervaCoimbra, 2000), ix-xxv.

<sup>8</sup> See João Rui Pita, "Um Livro com 200 Anos: A Farmacopeia Portuguesa (Edição Oficial). A Publicação da Primeira Farmacopeia Oficial: *Pharmacopeia Geral* (1794)," *Revista de História das Ideias* 20 (1999): 47-100; J. Conceição, J.R. Pita, M. Estanqueiro, & J.S. Lobo, "As Farmacopeias Portuguesas e a Saúde Pública," *Acta Farmacêutica Portuguesa* 3, no. 1 (2014): 47-65.

<sup>9</sup> *Pharmacopeia Geral* (Lisboa: Na Regia Officina Typografica, 1794), vol. 2, 91.

<sup>10</sup> *Ibid.*

As concerns medical prescriptions, there was harmony between the stipulations in the official Portuguese pharmacopoeia, under the influence of the *Edinburgh Pharmacopoeia*, and the medicines that were produced. Several among the formulations listed in *Pharmacopoeia Geral* were based on extractive processes, like *cozimento de quina composto* (compound brewed quina), *extracto de quina* (quina extract), *infusão fria de quina* (cold quina infusion), *tintura de quina composta* (compound quina tincture) and *vinho de quina composto* (compound quina wine).<sup>11</sup>

In addition to the pharmacopoeias also countless reference books mentioned quina. Without attempting to be exhaustive, in the 18<sup>th</sup> until the early 19<sup>th</sup> century several Portuguese authors and scientists showed interest in quina, its plantations, botanical, pharmaceutical, therapeutic, clinical, chemical studies, and so forth. The following works from the end of the 18<sup>th</sup> to mid-20<sup>th</sup> century are worthy of mention. First, the translation of Ralph Irving's work (*Experiments on the Red and Quill Peruvian Bark*) made in 1761 by António Felix Xavier de Paula, *Experimentos feitos na quina vermelha e amarella*.<sup>12</sup> Then, Fray José Mariano da Conceição Veloso (1742-1811),<sup>13</sup> a Brazilian religious, missionary, teacher and scientist who spent a time in Portugal (1790 to 1808) published *Quinografia portuguesa* (roughly translated as Portuguese studies on quina, 1799).<sup>14</sup> That work is a review of quina based on studies by other authors, in which varieties of quina and their medicinal applications are described. In 1801 José Ferreira da Silva published a translation of André Comparetti's work, entitled *Observações sobre a propriedade da quina do Brasil* (Observations on the property of the Brazilian quina,<sup>15</sup> which is a synthesis of the methods used to prepare various medicines with quina and their clinical application. That work was based on clinical studies, as also was Francisco Tavares' *Observações e reflexões sobre o uso proveitoso, e saudavel da quina na gota* (Observations and reflections on profitable and healthful use of quina in gout, 1802).<sup>16</sup> These relevant Portuguese scientific studies exemplify some of the most important interests vis-à-vis quina at that time, to wit, its botanical study and the demonstration of its therapeutic value beyond its febrifuge properties.

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<sup>11</sup> Ibid.

<sup>12</sup> Antonio F.X. de Paula, transl., *Experimentos feitos na quina vermelha e amarella* (Lisboa: Regia Of. Typográfica, 1761).

<sup>13</sup> On several aspects of Frey Veloso's life, see Márcia H.M. Ferraz, "A Produção do Salitre no Brasil Colonial," *Química Nova* 23, no. 6 (2000): 845-50.

<sup>14</sup> José M. Velloso, *Quinografia Portuguesa* (Lisboa: Na Officina de João Procopio Correia da Silva, 1799).

<sup>15</sup> Andre Comparetti, *Observações sobre a Propriedade da Quina do Brasil*, transl. José F. da Silva (Lisboa: Na Typographia Chalcographica e Litteraria do Arco do Cego, 1801).

<sup>16</sup> Francisco Tavares, *Observações e Reflexões sobre o Uso Proveitoso, e Saudavel da Quina na Gota* (Lisboa: Na Regia Officina Typografica, 1802).

### Production of medicines at University of Coimbra hospital pharmacy, Portugal, 18<sup>th</sup> and 19<sup>th</sup> centuries: case study

In 1772 the new statutes of University of Coimbra, the only university in Portugal until 1911,<sup>17</sup> accompanied innovations introduced in several European countries, resulting in the creation of two new schools (mathematics and philosophy) and several facilities devoted to teaching and research in the experimental sciences: school hospital, anatomical theatre, pharmaceutical dispensary, chemistry laboratory, botanical garden, physics cabinet, natural history cabinet and astronomic observatory.<sup>18</sup> The building of those new facilities sought to implement teaching of experimental sciences at the University, and several of them were directly related to the School of Medicine and medical education (from which pharmacy teaching then depended)<sup>19</sup> namely, the school hospital, anatomical theatre and pharmaceutical dispensary, directly related with medical education, while the chemistry laboratory and botanical garden, assigned to the School of Philosophy, contributed considerably, although in a less direct manner to the teaching of medicine.<sup>20</sup> Antonio Nunes Ribeiro Sanches (1699-1783) was one of the main personalities whom Francisco de Lemos (1735-1822), dean of University of Coimbra, called to advise him on the reform of the medical education. Strongly inspired by Hermann Boerhaave (1668-1738) Ribeiro Sanches insisted on that medical education had strong practical and experimental components. In addition to the teaching hospital, which was decisive, also other facilities corresponding to essential areas of medicine were necessary, for example, an apothecary, an anatomical theater, a botanical garden and a chemistry laboratory.

The pharmaceutical dispensary was the school hospital pharmacy.<sup>21</sup> It was meant to accomplish three general objectives: ground the practical teaching of pharmacy to medicine students, train graduate pharmacists and prepare medications for the patients admitted to the hospital and the general population in its role of public pharmacy. The pharmaceutical dispensary depended on the School of Medicine, and from the end of

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<sup>17</sup> The Marquis of Pombal was State Secretary of the Kingdom of Portugal and the Algarve (the equivalent to a present-day Prime Minister) during the rule of King Joseph I. Doubtlessly he was the most prominent minister in the government and implemented the reform of University of Coimbra in 1772; see Ana C. Araújo, ed., *O Marquês de Pombal e a Universidade*, 2<sup>nd</sup> ed. (Coimbra: Imprensa da Universidade de Coimbra, 2014); Rómulo de Carvalho, *História do Ensino em Portugal* (Lisboa: Fundação Calouste Gulbenkian, 1986).

<sup>18</sup> Rómulo de Carvalho, *A História Natural em Portugal no Século XVIII* (Lisboa: Instituto de Cultura e Língua Portuguesa, Ministério da Educação, 1987); Joaquim Ferreira Gomes, *O Marquês de Pombal e as Reformas de Ensino* (Coimbra: Livraria Almedina, 1982); Luís Reis Torgal, *Universidade, Ciência e "Conflito" de Faculdades no Iluminismo e nos Primórdios do Liberalismo Português* (Valencia: Sep. de Claustros y Estudiantes, 1989).

<sup>19</sup> João Rui Pita, ed., *Ciência e Experiência: Formação de Médicos, Boticários, Naturalistas e Matemáticos* (Coimbra: Imprensa da Universidade, 2006).

<sup>20</sup> See João Rui Pita, *Farmácia, Medicina e Saúde Pública em Portugal (1772-1836)* (Coimbra: Livraria Minerva, 1996).

<sup>21</sup> On the pharmaceutical dispensary, see João Rui Pita, "A Farmácia na Universidade de Coimbra (1772-1836): Ciência, Ensino e Produção de Medicamentos no Dispensatório Farmacêutico" (PhD dissertation, University of Coimbra, 1995).

the 18<sup>th</sup> to the beginning of the 19<sup>th</sup> century it grew to a large-size pharmacy. The professor of discipline materia medica and pharmacy was also the director of the pharmaceutical dispensary, while the daily management was entrusted to a pharmacist.

In 1850 the pharmaceutical dispensary prepared approximately 200 types of magistral formulæ and 200 officinal medicines per day, which was considered a high rate of production. The dispensary was close to the teaching hospital, having an internal connection to it, and was also open to the town general population. It operated at the older *Colégio de Jesus* (Jesus College); this building survived to this day, being property of University of Coimbra since the 18<sup>th</sup> century, when together with the 1772 University reform it was adapted to serve for the teaching of experimental sciences and as a hospital. The pharmaceutical dispensary became a strong competitor to the private pharmacies that served the general public.

We looked into the inventories of the pharmaceutical dispensary for the purchase of drugs for manufacture of medicines and the production of medicines at the hospital. After evaluating the use made of quina at the pharmaceutical dispensary we were able to establish that it was highly significant for a Portuguese pharmacy. From the end of the 18<sup>th</sup> and along the first two decades of the 19<sup>th</sup> century quina was the most used drug at the school hospital. As a rule, the American drugs played a very important role in the advancement of pharmaceutical science in Portugal.

The study we carried out with a sample of about 2,000 prescriptions made at the school hospital from 1772 to 1836 had the following results.<sup>22</sup> Regarding raw materials: 11 different drugs of animal origin, 22 of mineral and chemical origin and 120 of plant origin. The frequency of prescription was notably different: animal drugs were prescribed 81 times, mineral and chemical drugs 475 times and plant drugs 1,915 times. Thus the diversity of plant drugs used in medical prescriptions was significantly higher compared to the other types of drugs. Regarding the origin of plant drugs there is clear predominance of drugs from Europe and the Mediterranean basin. From a total of 120 different drugs, 78 were European or from the Mediterranean basin, 21 were African or from the East and 21 were American. However, the frequency in which the drugs appear in the prescriptions is not proportional to their origin. The frequency of prescription of American drugs exceeded the one of the European and Mediterranean basin drugs. The latter were prescribed 697 times, the African and Eastern drugs 439 times and the American drugs 779 times. We further found that all the prescribed drugs were listed in the first Portuguese official pharmacopoeia, *Pharmacopoeia Geral*, of 1794. Among the drugs of animal origin, egg yolk and honey were the most frequently prescribed, 36 and

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<sup>22</sup> In 1836 teaching at University of Coimbra was subjected to further reform by Minister Passos Manuel, within the context of a general reform of education in Portugal; see Luís Reis Torgal, & Isabel Nobre Vargas, "Vintismo e 'Instrução Pública': Imobilismo, Reformismo e Revolução," *Biblos* 59 (1983) 433-41; Luís Reis Torgal, "Passos Manuel e a Universidade: Do Vintismo ao Setembrismo," *Cultura - História e Filosofia* 6 (1987) 79-82; Luís Reis Torgal, & Isabel Nobre Vargas, "Produção e Reprodução Cultural," in *História de Portugal*, ed. José Mattoso (Lisboa: Círculo de Leitores, 1993), vol. 5, 685-96.

18 times, respectively. As concerns the drugs of mineral and chemical origin, *bitter cathartic salt* was the most frequently used, 126 times, followed by crude antimony and tincal, in 18 and 16 prescriptions, respectively. Relative to the drugs of plant origin and the ones from Europe and the Mediterranean basin, the most prescribed were manna ash (*Fraxinus ornus* L.), garden valerian (*Valeriana officinalis* L.) and chicory (*Cichorium intybus* L.) 80, 74 and 73 times, respectively. Among the African and Eastern drugs, the one most often used was rhubarb (*Rheum rhabarbarum* L.), 176 times, followed by tamarind, *Tamarindus indica* L.), 79 times, and camphor (*Cinnamomum camphora* (L.) J.Presl.) 71 times. Among the American drugs, quina dominated completely the prescriptions, 434 times. These figures show the importance given to this drug and reflect well its relevance in Western therapeutics. Quina also ranked first in the input-output balance (1819-1822) with a flow rate of 383\$485 *reis*,<sup>23</sup> and representing 22.6% of all prescribed drugs. The number of quina prescriptions is followed by the one of jalap (98 times), white sugar (50 times), ipecacuanha (43 times) and sarsaparilla (33 times).<sup>24</sup>

Many of the druggists that supplied drugs to pharmacies were Spanish and their emphasis was on American drugs. Druggists outside Coimbra often supplied drugs with better quality and lower price. Quina was a subject of scientific, medical and pharmaceutical, but also strong commercial interest. In a document from 1837 by Furtado Galvão, the director of the pharmaceutical dispensary observes that sometimes, and more particularly in the case of quina and marsh-mallow (*Althaea officinalis* L.) the Spanish druggists ought to be preferred over the Portuguese ones, because they sold the drugs for a lower price. In addition, some of the drugs came from the botanic garden of University of Coimbra.<sup>25</sup>

Quina was highly popular during the historical period we are considering. In the 18<sup>th</sup> century, *Água de Inglaterra* (English water), a very popular secret preparation that included quina, became famous in Portugal. Amongst the producers of *Água de Inglaterra*, Fernando Mendes (1647-1724) a physician from England, deserves mention, because he was the first to send it to Portugal, as also is Jacob de Castro Sarmiento (1692-1762) who distributed it in a highly enthusiastic and organized manner.<sup>26</sup>

<sup>23</sup> Réis (or reais) was the currency in Portugal from about 1430 to 1911, i.e., until the establishment of the republican regime.

<sup>24</sup> See Pita, "A Farmácia na Universidade de Coimbra (1772-1836)". The study was conducted with prescriptions made at the University Hospital preserved in the Archive of the University of Coimbra.

<sup>25</sup> Justification sent by the professor in charge of the Pharmaceutical Dispensary, Furtado Galvão, to the administration of the University; see Pita, "Farmácia na Universidade de Coimbra".

<sup>26</sup> About *Água de Inglaterra* in Portugal, see José P. Sousa Dias, *A Água de Inglaterra: Paludismo e Terapêutica em Portugal no Século XVIII* (Lisboa: Caleidoscópio, 2012); Patrick Figueiredo, "A 'Água de Inglaterra' em Portugal," in *A Circulação do Conhecimento: Medicina, Redes e Impérios*, ed. Cristiana Bastos, & Renilda Barreto (Lisboa: Imprensa de Ciências Sociais, 2011), 129-49.

**The Portuguese innovation: discovery of cinchonine – controversy between Coimbra and Lisbon scholars (1810-1812) regarding the isolation of cinchonine by B.A. Gomes**

In the beginning of the 19<sup>th</sup> century the Portuguese government sought to establish whether there was quina, or other plants with febrifuge properties in Brazil; commercial, economic and scientific issues were at stake. The University of Coimbra, school hospital, the Academy of Sciences of Lisbon and the Navy Hospital were charged of addressing this subject. In Lisbon, the work was undertaken by the physician Bernardino António Gomes (1768-1823), and in Coimbra one of the main protagonists in the analysis of quina was Tomé Rodrigues Sobral (1759-1829),<sup>27</sup> a chemistry professor. Gomes was one of the most respected doctors and scientists in Portugal at the turn of the 19<sup>th</sup> century. He had multiple scientific and clinical interests: he was the first Portuguese dermatologist, divulged the smallpox vaccine and had intense activity in the analysis of medicinal plants. Gomes attained positive results before Sobral. He isolated a substance - cinchonine - that was the first alkaloid extracted from quina, which he did from an alcoholic extract of gray quina, obtaining small cinchonine crystals.

Gomes' discovery led to enormous controversy. José Feliciano de Castilho (1769-1826) a professor at University of Coimbra school of medicine, refused to acknowledge the discovery arguing that it was impossible for Gomes to have attained such result. This was the trigger for a dispute between the two professors, significantly represented in *Jornal de Coimbra*,<sup>28</sup> and that eased off when Gomes moved to France, where he showed his results to French scientists, who acknowledged their validity.<sup>29</sup> Gomes had discovered crystals (cinchonine), as well as other crystalline formations different from the former and adhering to the walls of vessels, which he was unable to identify. Those crystals were finally identified in 1820 in Paris by Pierre-Joseph Pelletier (1788-1842) and Joseph B. Caventou (1795-1877): they were quinine.<sup>30</sup> Gomes was only one step away

<sup>27</sup> See Tomé Rodrigues Sobral, "Memoria sobre o Principio Febrifugo das Quinas," *Jornal de Coimbra*, 14, no. 82 (1819) 126-53. On Tomé Rodrigues Sobral, see A. M. Amorim da Costa, "Thomé Rodrigues Sobral (1759-1829): A Química ao Serviço da Comunidade," in *História e Desenvolvimento da Ciência em Portugal* (Lisboa: Academia das Ciências de Lisboa, 1986), vol. 1, 373-401.

<sup>28</sup> *Jornal de Coimbra* was a socio-professional journal with very strong ties to the School of Medicine of University of Coimbra.

<sup>29</sup> Among the Bernardino A. Gomes' works, see for example: "Extracto do Ensaio sobre o Cinchonino, e sobre sua Influencia na Virtude da Quina, e de Outras Cascas," *O Investigador Portuguez em Inglaterra* 2, no. 5 (1811) 36-43; "Observações Botanico-Medicas sobre Algumas Plantas do Brazil," *Memorias de Mathematica e Physica da Academia Real das Sciencias de Lisboa* 3, no. 1 (1812): 1-104; "Ensaio sobre o Cinchonino e sobre sua Influencia na Virtude da Quina, e de Outras Cascas," *Memorias de Mathematica e Physica da Academia Real das Sciencias de Lisboa* 3, no. 1 (1812): 202-17; "Resultados das Observações que Se Tem Feito sôbre as Virtudes da Casca 'Portlandia hexandra' Chamada Quina do Brasil," *Arquivos do Instituto de Farmacologia e Terapêutica Experimental* 1 (1931): 77-85.

<sup>30</sup> See A.M. Amorim da Costa, "A Química no I Colóquio sobre a História e Desenvolvimento da Ciência em Portugal. III- Alcalóides e Polímeros," *Boletim da Sociedade Portuguesa de Química* 23 (1986): 37-9; P. Rossignol, "Les travaux scientifiques de Joseph Pelletier," *Revue d'histoire de la pharmacie*, 281/282 (1989): 135-52.



from the main discovery: he had seemingly obtained quinine, but was unable to identify it! Quinine had antifebrile properties that were considerably more effective compared to cinchonine.

### Cinchonine and quinine in the scientific literature

Three official pharmacopoeias were published in Portugal during the 19<sup>th</sup> and first half of the 20<sup>th</sup> century: *Código Pharmaceutico Lusitano* (1835, 1<sup>st</sup> edition), *Pharmacopoeia Portuguesa* (1876) and *Farmacopeia Portuguesa* (1935, 1<sup>st</sup> edition); all of them included many medicines made of quinine.<sup>31</sup> In *Código Pharmaceutico Lusitano* (1835 and following editions), *Pharmacopea Portuguesa* (1876) and *Farmacopeia Portuguesa IV* (1935), quina or quinine are represented with adequate monographs; also quinine salts, the result of chemical laboratory work, are mentioned, as well as various formulations including quina and quinine.

*Código Pharmaceutico Lusitano*, namely, the second Portuguese official pharmacopoeia and authored by the physician Agostinho Albano da Silveira Pinto (1785-1852) includes a relevant monograph of cinchonine, perhaps as a function of Gomes' influence. Based on the work of François Magendie (1783-1855) in *Codex medicamentarius*, and the one by Noël-Étienne Henry (1769-1832), Nicolas J.-B.G. Guibourt (1790-1867) and Jean-Baptiste A. Chevallier (1793-1870) in *Manuel du Pharmacien* and *Pharmacopée Raisonnée*, Silveira Pinto described the processes for obtainment of quinine and cinchonine, attributing high value to Gomes' work. He observes that "cinchonine predominates [in grey quina] and quinine in yellow [quina], and in such amounts that it is believed that this [type of] quina does not contain [any] cinchonine"<sup>32</sup>. In regard to quinine he wrote: "that principle is more energetic than this one [cinchonine]"<sup>33</sup>. Concerning red quina he stated that "it is the most energetic among all the [varieties of] quina"<sup>34</sup>, to the point that it contained twice the amount of quinine as yellow quina. It should be noted that the monographs on quinine sulfate and cinchonine sulfate, being the last ones are quite extensive and detailed. The obtainment of those salts and the mentions to active principles in the pharmacopoeias clearly show their attunement to the latest advances in chemistry, namely, the isolation of active principles from plants, alkaloids in particular. This situation marked a new era in the history of pharmacy. In the formulary of *Código Pharmaceutico Lusitano* there are various mentions to preparations using quina and quinine.

<sup>31</sup> We allude to the first editions of the pharmacopoeias only.

<sup>32</sup> Agostinho A. da Silveira Pinto, *Código Pharmaceutico Lusitano* (Coimbra: Na Imprensa da Universidade, 1835), vol. 2 (Pharmacopéa), 75.

<sup>33</sup> Ibid.

<sup>34</sup> Ibid.

*Pharmacopéa Portugueza* (1876)<sup>35</sup> contains an extensive monograph on quina,<sup>36</sup> in which three types are described: yellow, grey (sometimes mixed with pale quina) and red quina with their botanical characterization; also the doses of quinine are indicated. This work further includes a small monograph on quinine, cinchonine and various salts, such as neutral sulfate of quinine and quinine valerate. This pharmacopoeia was used along three decades to be replaced by *Farmacopeia Portuguesa* in 1935.<sup>37</sup> In the latter, the monograph on quina describes the yellow and red varieties and recommends using yellow quina in the cases when the red one is not specifically indicated.<sup>38</sup> It also mentions the laboratory methods for total dosing of alkaloids and dosing of quinine. Various medicines included in the *Farmacopeia Portuguesa* contain quina and quinine, such as, e.g., *quina wine*, *brewed quina*, *quina tincture* and *injectable solute of quinine basic chlorhydrate*.

The discovery of quinine by Pelletier and Caventou in 1820 provided the reason for the febrifuge properties of quina. Following the discovery of this alkaloid, the therapeutic and commercial value of quina increased substantially. This accounts for the fact that after mid-19<sup>th</sup> century some of the more remarkable works in the Portuguese scientific literature dealt with quina plantations outside the Americas and the quinine extractive industry. Those subjects were of much interest to Portugal, since it had colonies in Africa (Cape Verde, Guinea, São Tomé and Príncipe, Angola and Mozambique) and Asia (India and Timor). In 1864, Bernardino Barros Gomes (1839-1910), a grandson of Bernardino A. Gomes Sr., forester engineer and botanist, spent a season studying in Germany and published the work *A Cultura das Plantas que Dão a Quina* (Cultivation of plants that yield quina)<sup>39</sup> where he describes the best conditions to cultivate the plants. In 1864, the physician Joaquim H. da Cunha Rivara (1809-1879) translated from English William Graham McIvor's work, *Memoria sobre a Propagação e Cultura das Chinchonas Medicinaes, ou Arvores de Quina do Peru* (Notes on the Propagation and Cultivation of the Medicinal Cinchonas, or Peruvian Bark Trees).<sup>40</sup> Júlio Augusto Henriques (1838-1928), remarkable Portuguese botanist, professor at University of Coimbra and director of the University botanic garden, published *Instruções Práticas para a Cultura das Plantas que Dão a Quina* (Practical instructions for the cultivation of plants that yield quina, 1880) and *Instruções praticas para culturas coloniaes* (Practical instructions

<sup>35</sup> *Pharmacopéa Portugueza* (Lisboa: Imprensa Nacional, 1876) is the first official pharmacopoeia written by a specialized committee composed of physicians and pharmacists; Bernardino António Gomes Jr. was the president of this committee.

<sup>36</sup> *Ibid.*, 348-50.

<sup>37</sup> *Farmacopeia Portuguesa. Edição Oficial* (Lisboa: Imprensa Nacional de Lisboa, 1935). The replacement of the pharmacopoeia from 1897 is a complex subject. That work had become outdated; physicians and pharmacists had long advocated for a modern and up-to-date pharmacopoeia, but only in 1935 it was replaced by a new one attuned to the rules of the New Political Regime of the *Estado Novo* (the political regime from 1926 to 1979).

<sup>38</sup> *Ibid.*, 433-4.

<sup>39</sup> Bernardino Barros Gomes, *Cultura das Plantas que Dão a Quina* (Lisboa: Imprensa Nacional, 1864).

<sup>40</sup> William Graham McIvor, *Memoria sobre a Propagação e Cultura das Chinchonas Medicinaes, ou Arvores de Quina do Peru* (Nova-Goa: Imprensa Nacional, 1864).

for colonial crops, 1884).<sup>41</sup> In them he called the attention to the relevance of selecting the best species of quina for cultivation, for which purpose he listed the appropriate authorities. In 1936 Fausto Landeiro (1896-1948) published in *Boletim Geral das Colónias* the study *A Quina e os Seus Derivados* (Quina and its derivatives)<sup>42</sup> which reflected the relevance of quina as a scientific and economic asset.

Particular importance was given to the study of quina at the School of Pharmacy of University of Coimbra, being the references Aloísio Fernandes' *Do Valor Alcalóidico das Quinas de S. Tomé* (On the alkaloid value of quina from S. Tomé, 1940-41),<sup>43</sup> *A Introdução da Cultura das Quinas nas Nossas Províncias Ultramarinas e a Participação dos Portugueses no Seu Estudo Químico* (Introduction of quina cultivation in our overseas provinces and the Portuguese's co-participation in their chemical study, 1940)<sup>44</sup> and *O Problema das Quinas* (The quina problem, 1944),<sup>45</sup> and José Cardoso do Vale's *Dosagem dos Alcalóides das Quinas* (Dosage of quina alkaloids, 1941).<sup>46</sup>

In *Do Valor Alcalóidico*, Fernandes Costa points to the relevance of quina and quinine in therapeutics, while calling the attention to the lack of care with the plantations in the Portuguese ex-colonies. He makes mention of the low quality of the quinine salts obtained, stating that they only served to prepare medicines for poor malaria patients.<sup>47</sup> In this regard it is worth to notice that the laboratory of pharmacognosy of University of Coimbra School of Pharmacy developed from the 1930s to 1970s a dynamic program of research on raw materials of pharmaceutical interest originated in the former Portuguese colonies. Research at the laboratory had various sources of funding, being the main one *Fundo Sá Pinto* (Sá Pinto Fund) by the banker

<sup>41</sup> Júlio Augusto Henriques published several studies on quina and botany relative to the Portuguese ex-colonies: "A Cultura das Plantas que Dão a Quina nas Possessões Portuguezas," *O Instituto*, 22 (1876): 184-90; "A Cultura das Quinas na Africa Portuguesa," *Jornal de Horticultura Pratica* 9 (1878): 45-7; "A Sementeira da Cinchona," *Jornal de Horticultura Pratica* 11 (1880): 134-7; *Instruções Praticas para a Cultura das Plantas que Dão a Quina* (Coimbra: Imprensa da Universidade, 1880); "A Propósito da Cultura das Plantas que Dão a Quina," *Jornal de Horticultura Pratica* 13 (1882): 26-7; *Instruções Praticas para Culturas Coloniaes* (Coimbra: Imprensa da Universidade, 1884); "Instruções sobre a Cultura das Especies Anilíferas em Angola," *As Colonias Portuguezas* 3 (1889): 23-4; "Da Coca e da Sua Cultura," *As Colonias Portuguezas* 10 (1890): 76-7; "Das Plantas Productoras da Borracha," *Portugal em África* 33 (1896): 353-81; "Cultura das Plantas do Anil e Processos de Preparação d'esta Materia Corante," *Portugal em África* 41 (1896): 204-12; and *Agricultura Colonial: Meios de A Fazer Progredir* (Lisboa: A. Liberal, 1901).

<sup>42</sup> Fausto Landeiro, *A Quina e os Seus Derivados* (Lisboa: Gráfica Bertrand, 1936).

<sup>43</sup> See Aloísio Fernandes Costa, "Do Valor Alcalóidico das Quinas de S. Tomé," *Notícias Farmacêuticas* 7 (1940/1941): 173-89.

<sup>44</sup> See Aloísio Fernandes Costa, *A Introdução da Cultura das Quinas nas Nossas Províncias Ultramarinas e a Participação dos Portugueses no Seu Estudo Químico*. (Coimbra: Comunicação ao Congresso de História da Actividade Científica Portuguesa, 1940). This is a paper presented, in 1940, at the Congress of History of the Portuguese Scientific Activity (*Congresso do Mundo Português*), which by itself reveals the interest of this study for the Portuguese scientific planning and colonial issues.

<sup>45</sup> Aloísio Fernandes Costa, *O Problema das Quinas* (Lisboa: Cosmos, 1944).

<sup>46</sup> José Cardoso do Vale, "Dosagem dos Alcalóides das Quinas (Sôbre os Métodos Preconizados pela Farmacopeia Portuguesa, 1936)," *Notícias Farmacêuticas* 7 (1941) 433-48.

<sup>47</sup> Fernandes Costa, "Do Valor Alcalóidico," 188.

Cândido Sotto Mayor, followed by *Instituto de Alta Cultura* (Institute of High Culture) and *Junta de Investigações do Ultramar* (Overseas Research Committee). The work carried out by *Agrupamento de Farmacognosia da Junta de Investigações do Ultramar* (Pharmacognosy group of the Overseas Research Committee) since 1959 is noteworthy and demonstrates the huge interest of the Portuguese government in the analysis of products from its former colonies in Africa.<sup>48</sup>

### **Industrial investment in quina plantations in Portuguese colonies and in the implementation of a quinine extraction industry in Portugal**

The success meant by the isolation of quinine and the preparation of medicines based on quinine salts was decisive to increase the investment in quina plantations for industrial exploitation. Therefore various studies of quina and quinine were performed in the course of the second half of the 19<sup>th</sup> century.<sup>49</sup>

The interest in establishing quina plantations away from the plant natural habitat started in the 18<sup>th</sup> century. However, it was not always fruitful, while several authors called the attention to the disadvantages of the forest destruction that resulted from such practice.<sup>50</sup> The colonial empires sought to establish plantations outside South America to guarantee sufficient raw material to obtain the product in industrial scale. In the first half of the 20<sup>th</sup> century, the industry of quinine was a source of enormous wealth for several countries. Plantations were established in the Far East - Ceylon, India and Java – and there were also attempts to create plantations in Congo, Formosa, Brazil, São Tomé and Príncipe, Cape Verde and Angola. The English plantations in India represented about 2.5% of the market. The French established plantations in Algeria and Madagascar and Belgium in Congo. The Germans planted quina in Tanganyika. The plantations introduced by the Dutch in Java and Sumatra at the beginning of the 20<sup>th</sup> century became famous, because they provided about 97% of the quina in the market. Under the protection of the Dutch government, the Cinchona Convention was established, which

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<sup>48</sup> The scientific production about *quina*, quinine and other American drugs are the focus of ongoing research by these authors and is not a topic of discussion in the present paper. In this regard, see, for instance, Célia Cabral, João Rui Pita, & Lígia Salgueiro, *Plantas Mediciniais: Entre o Passado e o Presente: A Coleção de Fármacos Vegetais da Faculdade de Farmácia da Universidade de Coimbra (Séculos XIX-XX)* (Coimbra: Imprensa da Universidade de Coimbra, 2014).

<sup>49</sup> Scientific issues related with the use of quinine for the treatment of malaria are not a topic of discussion in the present article; that subject has been widely addressed in the Portuguese and international literature, see, for example, a recent article by André F.C. da Silva, & Jaime L. Benchimol, "Malaria and Quinine Resistance: A Medical and Scientific Issue between Brazil and Germany (1907–19)," *Medical History* 58, no. 1 (2014): 1-26.

<sup>50</sup> Fernandes Costa, *Problema das Quinas*, 18-9.

ensured Holland the monopoly of the cultivation of quina, the setting of its price and the provisioning of underprivileged areas of the world.<sup>51</sup>

Also Portugal attempted to plant quina. Let us review some relevant milestones. In 1864 Mendes Leal, the Navy Minister, obtained in Java 30,000 seeds of *Cinchona pahudiana* Howard, a species that does not entail any guarantee of success and, indeed, the results were insignificant. In addition, as this species of quina has very low quinine content, less than 20% of the total alkaloids, compared to *C. succirubra* Pav. ex Klotzsch, its market value was insignificant. In 1867 the well-known physician and scientist, Gomes Jr., presented a quina species (*C. succirubra*) with greater quinine content to the botanical garden of University of Coimbra. The botanical garden was directed by Júlio A. Henriques, who had ordered seeds of various species from different countries: India, Ceylon, Java, Australia, France, etc. Thus seeds of various species came to enrich the collection of the botanical garden.

In 1869 quina was introduced into the Portuguese territory from the Cape Verde colony, after the plantations had been extended to Madeira - and in 1871 also to São Tomé and Príncipe. This was not only a scientific issue, but also had implications for the country's economy, for which reason the Portuguese government became involved, sending letters to the governors of those territories concerning the cultivation of quina.<sup>52</sup> The species introduced in Portugal were: *C. calisaya* Wedd., *C. calisaya* var. *ledgeriana* Howard, *C. succirubra* and *C. officinalis* L. Since the end of the 1860s Júlio A. Henriques had been the main promoter of the expansion of the quina plantations in the Portuguese colonies in Africa, having carried out several studies on the quality of the plants. Encouraged by him the botanical garden of University of Coimbra sent 1,183 plants and enormous amounts of seeds to the colonies, to wit, Cape Verde and São Tomé, along more than ten years.<sup>53</sup> Nevertheless, Portugal did not want to restrict the cultivation of quina to its colonies in Africa, but also attempted to cultivate it in Madeira and the Azores. A proposal was made for Portugal to be allowed planting cinchona in Madeira, the Azores, Cape Verde and São Tomé, since the bark could thus be sent more easily to German, English and French industries, compared to the plantations in the Middle East and South America.<sup>54</sup> In 1872, J.A. Simões de Carvalho (1822-1902), naturalist and professor at the School of Philosophy of University of Coimbra, discussed the quina plantations in the Algarve. Carvalho tells that 100 plants of *C. succirubra* obtained by seed germination had been distributed across the Portuguese colonies in 1869, and that by 1872 there were many plants of that species at the University botanic garden "in

<sup>51</sup> Ibid., 20-53. See Louis H. Destoches, *A Quinina na Terapeutica* (Amsterdam: Repartição para o fomento do uso da quinina, 1931), translated by the pharmacist Emílio Fragoso.

<sup>52</sup> See José E. Mendes Ferrão, *A Aventura das Plantas e os Descobrimentos Portugueses* (Lisboa: Instituto de Investigação Científica Tropical, 1992), 130. That author had as basis the study by J.C. Guimarães, *Algumas Indicações sobre as Plantas que Dão a Quina* (Lisboa, 1892).

<sup>53</sup> See Fernandes Costa, *Problema das Quinas*, 54.

<sup>54</sup> Ibid.

various developmental stages, and soon they will be fit to be sent to the colonies, to the Azores, and the Algarve, so as to propagate this much useful plant".<sup>55</sup>

In 1874 Joaquim dos Santos e Silva (1842-1906) performed chemical analyses of quina sent by the physician Jacinto de Sousa Ribeiro from Cape Verde.<sup>56</sup> Santos e Silva, a respected chemist, was a professor at the School of Pharmacy of University of Coimbra. He devoted part of its scientific life to chemical analysis focusing on water and food. Júlio A. Henriques encouraged Santos e Silva to perform the analysis of quina from São Tomé, which resulted in the publication, in 1876, of an interesting work entitled *Breve Notícia sobre a Riqueza das Quinas nas Possessões Portuguezas da Africa* (Short notice of the wealth of quina species in the Portuguese possessions in Africa)<sup>57</sup> in which he highlighted the relevance of this natural product.

In 1880 Júlio Henriques called the attention to the need to carry out a pondered study of the species to be cultivated in order to make the greatest profit from quinine. The settlers in the Portuguese colonies were not especially interested in the cultivation of quina, but rather in other products, such as coffee, for which they received incentives and dividends from the government. Between Cape Verde and São Tomé, the latter was the main focus of the Portuguese interest, as the tests performed in Cape Verde had not been much successful. In Aloísio Fernandes Costa's opinion, "the attempts at establishing a new [source] of wealth had been more audacious"<sup>58</sup> in São Tomé. Facing a coffee crisis, the peasants looked back to the relevance of cultivating quina and extracting quinine and decided to invest in them. From 1875 to 1887 the quina plantations in São Tomé increased from 31 to 1,600,000.<sup>59</sup> It was there that the cultivation of quina in Portuguese territory achieved its best results, ensuring the supply to the national market, as well as reasonable exports. Nevertheless, the income from quinine was low and the quinine extraction industry did not flourish in Portugal to all but disappear after the First World War. Three factors were decisive in that disastrous enterprise: a) quina plantations were fostered in large-scale in Portugal when they were already very powerful at the international level; b) no detailed study was performed to select the most suitable species, but *C. succirubra* was chosen because it grew faster, although it was not the richest in quinine; c) several hybrid species were grown.

<sup>55</sup> See Joaquim A. Simões de Carvalho, *Memoria Historica da Faculdade de Philosophia* (Coimbra: Imprensa da Universidade, 1872), 240.

<sup>56</sup> See José E. Mendes Ferrão, "Na Linha dos Descobrimientos dos Séculos XV e XVI: Intercâmbio de Plantas entre a África Ocidental e a América," *Revista de Ciências Agrárias* 36, no. 2 (2013): 250-69.

<sup>57</sup> Joaquim dos Santos e Silva, "Breve Notícia sobre a Riqueza das Quinas Cultivadas nas Possessões Portuguezas da África," *O Instituto* 22 (1876): 184-97. See João Rui Pita, *A Escola de Farmácia de Coimbra (1902-1911)* (Coimbra: Imprensa da Universidade de Coimbra, 2009), 59-60.

<sup>58</sup> See Fernandes Costa, *Problema das Quinas*, 55.

<sup>59</sup> It should be observed that Count Ficalho, in *Plantas Úteis da África Portuguesa* (Lisboa: Imprensa Nacional, 1884) judged enthusiastically the cultivation of quina in São Tomé; his work had a 2<sup>nd</sup> edition in 1947, with foreword by Ruy Telles Palhinha.

The content of Silva Machado's paper "*Quina nas Colonias Portuguezas* (Quina in the Portuguese colonies, 1882) is quite interesting.<sup>60</sup> There he made a summary of the quina plantations in São Tomé (belonging to the farmer Dias Quintas) and Cape Verde, judging the state of affairs in an optimistic light, as "the quina [species] in S. Tomé are very rich in alkaloids and not inferior at all to the best ones in English and Dutch possessions"<sup>61</sup>. He further listed the cultivated species: *C. succirubra*, *C. josephiana* (Wedd.) Wedd. and *C. calisaya*. Silva Machado was very clear upon asserting, almost at the end of the paper, that "it is highly probable that when quina comes from our colonies in large amounts, it will not be long before the manufacture of quinine sulfate will be attempted, which might then be achieved with good pricing conditions, not only for internal consumption, but also in Africa and Brazil"<sup>62</sup>.

However, the scientific proofs presented by Júlio A. Henriques and his suggestions on the species to be planted were not considered by the farmers, who rather preferred a species of faster growth, albeit with lower quinine content. Neither the advice on the most appropriate altitude and fields for plantations was followed. In 1944, Aloísio Fernandes Costa, resuming the analysis of the quina from São Tomé, sought to analytically account for the failure of the local quina. He observed that most of the samples received were of *C. calisaya* and *C. succirubra* and a very small amount of *C. ledgeriana*, the quinine content of all of which was low, even though in theory the one of *C. ledgeriana* ought to be high.<sup>63</sup> On those grounds he put forward the following hypothesis: "Might it be a denatured product, perhaps due to unknown hybridizations, or a mistake in identification?"<sup>64</sup>.

Being the quinine content of plants grown in São Tomé poor, the extraction industry could not be but weak. Four quina producers (João da Costa Pedreira, Nicolau José da Costa, Frederico Bister and Dias Quintas) and a pharmacist (João António Rosa) founded in 1890, in Lisbon, the *Sociedade Luso-Africana* (Luso-African Society). In 1875 José Júlio Rodrigues, a chemistry professor at the Lisbon Polytechnic School, mentioned the need of a factory for that purpose. Ribeiro da Costa & C<sup>a</sup> purchased the equipment of *Sociedade Luso-Africana* after its closure and continued the production of quinine salts. That situation remained until the end of World War I (1914-1918). The Portuguese and international economic context, the Dutch monopoly on quina and the settlement of the

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<sup>60</sup> Silva Machado, "A Quina nas Colonias Portuguezas," *Jornal da Sociedade Pharmaceutica Lusitana* (1882): 251-7.

<sup>61</sup> *Ibid.*, 251.

<sup>62</sup> *Ibid.*, 257.

<sup>63</sup> In the Historical-Pharmaceutical Heritage collection, School of Pharmacy, University of Coimbra, there are 21 bags containing quina bark from São Tomé and Príncipe.

<sup>64</sup> See Fernandes Costa, *Problema das Quinas*, 62.

main quina producers in the Far East (Java) were determinant for the end of the Portuguese plantations, quinine extractive industry and production of its salts.<sup>65</sup>

### Conclusions

Just as in other European countries, quina was a drug of great importance for medical therapeutics in Portugal. In addition, it was an object for thorough botanical and chemical studies, as well as for commercial and industrial investment. The study presented here represents a systemization of four great chapters of the history of quina and quinine in Portugal, the understanding of which is still in progress.

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<sup>65</sup> The problems associated with quina during World War II (1939-1945) were a subject of great interest following the occupation of the Netherlands by the Germans and the control of Indonesia by the Japanese.