

## **Cinchona bark and quinine in the Portuguese official pharmacopoeias (1794–2001)**

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*Cinchona* bark (bark from plants of the genus *Cinchona* with antimalarial activity) and its alkaloid quinine were widely used to treat intermittent fevers. This paper aims to quantitatively analyze the presence of *Cinchona* bark, quinine and other *Cinchona* bark-derived substances in the Portuguese official pharmacopoeias published between 1794 and 2001. The analysis showed that the *Pharmacopêa Portuguesa* (1876) is the Portuguese official pharmacopoeia with the highest percentage of medicines containing *Cinchona* bark (2.61%). The *Farmacopoeia Portuguesa IV* (1935) is the official pharmacopoeia with the highest percentage of quinine-containing medicines (2.34%). Medicines made from *Cinchona* bark are present in the Portuguese official pharmacopoeias until the *Farmacopoeia Portuguesa IV* (1946). Medicines made from quinine have been present in Portuguese official pharmacopoeias since the *Código Pharmaceutico Lusitano* (1835).

### **1. Introduction**

In Portugal, the term “quina” is used to designate the bark of several species of plants belonging to the genus *Cinchona* that possess antimalarial properties (Cabral et al. 2014 p. 127). There are 23 accepted species within the genus *Cinchona* (Andersson 1998). Plants of the genus *Cinchona* are native to South America (Costa 1944). By the 17th century the bark of the *Cinchona* tree was exported to Europe and it was used to treat intermittent fevers (Crawford 2016). Due to the characteristic episodes of intermittent fever that malaria can cause, such as the so-called tertian and quartan fevers (Jarcho 1993; Andrés Turrión 2005), medical historiography associated intermittent fevers with malaria (Oaks Jr. et al. 1991). Due to *Cinchona* bark’s important therapeutic role, *Cinchona* plants were acclimatised to Asia and Africa (Costa 1944).

*Cinchona* bark may contain several substances for therapeutic use, of which the alkaloid quinine is seen as the most important (Nair 2010). Quinine was isolated in 1820 by French scientists Joseph Pelletier (1788–1842) and Joseph-Bienaimé Caventou (1795–1877) (Pelletier and Caventou 1820). Soon after it was used to treat intermittent fevers (Double 1820). In addition, pharmacology studies on quinine were performed (Magendie 1821a, b; Chomel 1821), which pointed to the same “medical properties” of quinine as of the bark of the *Cinchona* tree (Magendie 1821b, p. 38-39). Quinine was used for its febrifuge properties by the military and civilians (Gachelin 2017) and supported colonisation by offering protection to Europeans on malaria-endemic territories (Magner 2005). *Cinchona* bark reinforced trade routes (Gänger 2015) and fostered *Cinchona* plantation for the production of quinine (Van der Hoogte and Pieters 2014). It is worth noting the Dutch monopoly in the production and trade of *Cinchona* bark and quinine (established in the 1920s), which ended after the Second World War (Van der Hoogte and Pieters 2016; Cuvi 2011). *Cinchona* bark (Sarmiento 1756; Tavares 1802) and quinine (Saint-Laurent 1842; Davidson and Birt 1938; Loeb 2005) were used to treat several diseases, including gout (Tavares 1802) and influenza (Loeb 2005 p. 210; Rebelo-de-Andrade and Felismino 2018). Currently, quinine is one of the therapeutic options for malaria (Moore 2018).

Several authors have underscored the importance of *Cinchona* bark and quinine in medicine and therapeutics (Lemos 1899; Laín

Entralgo 1978; Greenwood 1992; Brockway 2002; Magner 2005; Webb Junior 2009). *Cinchona* bark and quinine share a remarkable, multifaceted story, with interesting controversies (Oliveira 2009). The importance of *Cinchona* bark and quinine to medicine and pharmacy can be measured in several ways. The reference to *Cinchona* bark and quinine in medical and pharmaceutical literature is one of them. Other ways to assess *Cinchona* bark and quinine’s role in medicine and pharmacy include the analysis of prescriptions, drug sales, etc.

Portuguese historiography has few studies on the presence of *Cinchona* bark and quinine in medical and pharmaceutical literature. João Rui Pita conducted a qualitative and quantitative analysis of the first official Portuguese pharmacopoeia, *Pharmacopoeia Geral* (1794) (Pita 1999). He found that there were two monographs on *Cinchona* bark and several medicines made from it (Pita 1999). In another paper by Cabral et al. (2015), there are notes on the monographs on quinine, cinchonine and *Cinchona* bark in the first editions of the Portuguese official pharmacopoeias published until 1935. It also addresses the presence of medicines containing quinine in *Código Pharmaceutico Lusitano* (1835), *Pharmacopêa Portuguesa* (1876) and *Farmacopoeia Portuguesa IV* (1935) (Cabral et al. 2015). There are also several studies on a medicine made from *Cinchona* bark, *Água de Inglaterra* (Water of England) (Esaguy 1931; Esaguy 1936; Esaguy 1937; Vilhena 1932; Pina 1940; Figueiredo 2011; Dias 2012). *Água de Inglaterra* was an important medicine sold in Portugal from the 17<sup>th</sup> to the 19<sup>th</sup> century (Dias 2012). The Portuguese physician based in England, Jacob de Castro Sarmiento (1691-1762) was well-known for the preparation of this medicine (Dias 2012). Augusto d’Esaguy highlights that the *Água de Inglaterra* was mentioned in all pharmacopoeias published between 1681 and 1821 (Esaguy 1936). José Pedro Sousa Dias refers to the almost omnipresence of *Água de Inglaterra* in the work of Jacob de Castro Sarmiento (Dias 2012). Dias provides data on the representation of the *Água de Inglaterra* in the books *Materia Medica* and *Do uso e abuso das minhas agoas de Inglaterra*, both written by Castro Sarmiento (Dias 2012). Dias also points to references to the *Água de Inglaterra* in the book *Considerações médicas* (1758) by the physician João Mendes Sachetti Barbosa (1714-1774) (Dias 2012).

Concerning the study of medical prescriptions in Portugal, 1954 medical prescriptions prepared in the *Dispensatório Farmacêutico* (the apothecary of the University of Coimbra Teaching Hospital) drawn up between 1779 and 1825 have been analysed (Fig. 1). *Cinchona* bark was prescribed in 434 of the prescriptions analysed (Pita 1995), which is indicative of its therapeutic importance in Portugal.

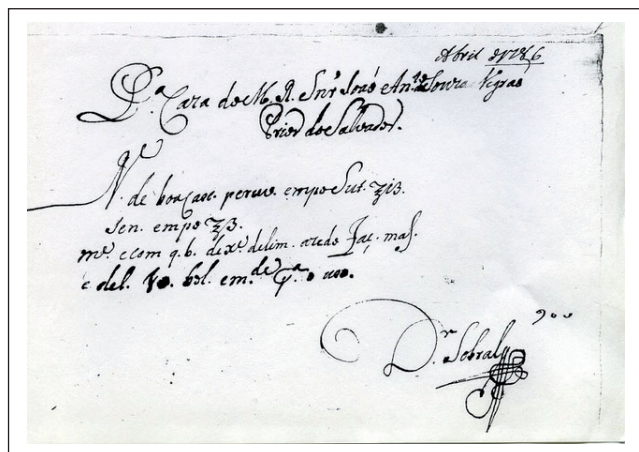


Fig. 1: Medical prescription with *Cinchona* bark dated 1786 and prepared at the apothecary of the University of Coimbra Teaching Hospital (In: Arquivo da Universidade de Coimbra, Portugal).

Our study seeks to quantitatively assess the presence of *Cinchona* bark, quinine and other substances obtained from *Cinchona* bark in all official Portuguese pharmacopoeias published from the 18<sup>th</sup> to the 20<sup>th</sup> century. This quantitative study will make it possible to infer the theoretical therapeutic importance of *Cinchona* bark and quinine in Portugal during the period analysed. The official pharmacopoeias set standards for the production of medicines, i.e., they provide guidelines on the control of the raw materials used to produce medicines, and on the quality control of medicines. The issue at stake in our study is the way *Cinchona* bark, quinine, and the medicines that contain them were officially recognised in Portugal, given that *Cinchona* bark and quinine are among the most important pharmaceuticals in the history of pharmacy and medicine.

## 2. The Portuguese official pharmacopoeias (1794-2001): brief outline

Pharmacopoeias are official books that list the medicines approved in a given country or geographical area, and the raw materials used to prepare such medicines. They lay down methods of analysis and establish quality standards for medicines and their raw materials. They provide the legal framework developed by national or regional committees or authorities (Conceição et al. 2014).

In Portugal, the first pharmacopoeia in the Portuguese language and written by an apothecary (who was also a priest), D. Caetano de Santo António (Pita 1995) was published in 1704, the *Pharmacopoea Lusitana*. However, like other pharmacopoeias published in the 18<sup>th</sup> century in Portugal, this was not an official pharmacopoeia (Tello da Fonseca 1938 p. 156), i.e., it was not sanctioned by the government and adopted by the country overall. This pharmacopoeia was essentially galenic and did not include drugs of American origin (such as *Cinchona* bark) in the monographs of the listed drugs, although they did exist in some of the registered formulas. This work is a landmark in the history of Portuguese pharmacy. There were three more editions, one of which was published posthumously and already included some chemical medication.

The first official Portuguese pharmacopoeia, *Pharmacopoeia Geral* (Fig. 2) was published in 1794 by Francisco Tavares (1750-1812). Tavares was a physician, who also taught Medicine and Pharmaceutical Art at the Faculty of Medicine of the University of

Coimbra. He was chief physician of the Kingdom ruled by Maria I. The book is not signed, but research has shown he is the author of that pharmacopoeia (Pita 1995). It was sponsored by the Faculty of Medicine of the University of Coimbra, in accordance with the Statutes of the University (1772), which mandated the faculty to publish an official pharmacopoeia. The publication of an official pharmacopoeia followed the standardising trend of medical and pharmaceutical Enlightenment, therefore provided “unequivocal proof of a new view of the physical, organic and moral state of the population: an *enlightened political* view that aspired to the hygienic control of the social body through transparent and uniform practices sovereignly dictated” (Pereira and Pita 1993 p. 462). The publication of the first official pharmacopoeia in Portugal was in line with events in other European countries. It was a galenic and chemical pharmacopoeia, although it did not adopt Lavoisier’s modern chemistry, due to the time-lag between the drafting and publication thereof. This pharmacopoeia was published again later (in 1823 and 1824) without having changed significantly.

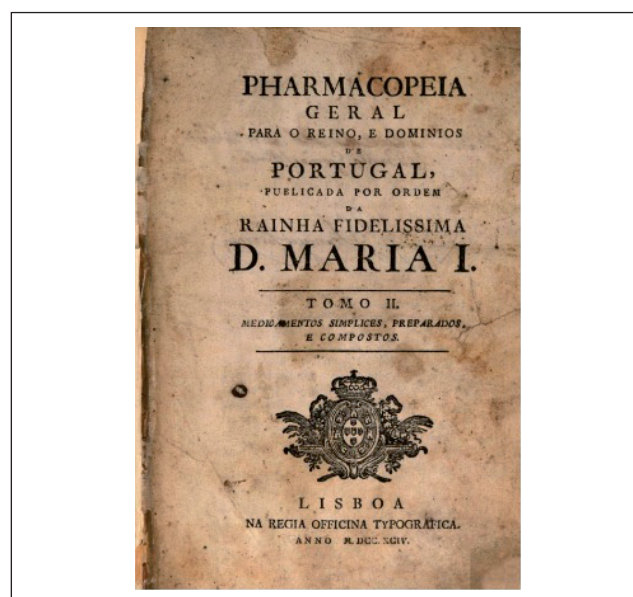


Fig. 2: Frontispiece of the second volume of the first Portuguese official pharmacopoeia, *Pharmacopoeia Geral* (1794), authored by Francisco Tavares (1750-1812).

The second official pharmacopoeia, *Código Farmacêutico Lusitano*, was also written by a physician, Agostinho Albano da Silveira Pinto (1785-1852). Pinto was a doctor in the city of Porto, as well as a teacher and politician. The pharmacopoeia was published first in 1835. After writing this pharmacopoeia, the author himself proposed to the University of Coimbra to use it to replace the outdated *Pharmacopoeia Geral*. It was properly assessed, adaptations and extensions were suggested, and it was adopted as the official pharmacopoeia in 1835. At that time, the University of Coimbra was still responsible for developing the official Portuguese pharmacopoeia. The *Código Farmacêutico Lusitano* was declared the official Portuguese pharmacopoeia by Decree of 6 October 1835, which added that it should include a “part on Pharmacography” as a supplement. This complementary work, published in 1836, was called *Pharmacographia do Código Farmacêutico Lusitano* (Pinto 1836a). *Código Farmacêutico Lusitano* was a very complex pharmacopoeia, which did not follow the traditional structure of a pharmacopoeia. However, in scientific and technical terms it was very up to date, and included active principles extracted from plants. These active principles were one of the great pharmaco-therapeutic highlights of the first half of the 19<sup>th</sup> century.

*Código Farmacêutico Lusitano* was published 6 times, twice posthumously (Conceição et al. 2014 p. 48). The posthumous

editions were organised and revised by the physician José Pereira Reis (1808-1887). The sixth and last issue of the *Código Farmacopoeia Lusitano*, published in 1876, was no longer the official pharmacopoeia. *Código Farmacopoeia Lusitano* was also “temporarily” declared “Legal pharmaceutical code of the Brazilian empire” (Pinto 1841 p. xv; Pinto 1846 p. xv). The *Código Farmacopoeia Lusitano* was difficult to use and interpret, and it lacked a section dedicated to monographs on raw materials, which made it quite unpopular among doctors and pharmacists. It should also be remembered that the first edition of the *Código Farmacopoeia Lusitano* was published a year before the reform of pharmacy education in Portugal, i.e., in the middle of a period of profound changes in the Portuguese education system implemented by Passos Manuel. Under the reform the Pharmacy Schools of Coimbra, Lisbon, and Porto were created in 1836, alongside the Medical and Surgical Schools of Lisbon and Porto. It was also published during the public health reforms that were carried out in Portugal in the first half of the 19<sup>th</sup> century. It should be noted that in 1838 Queen Maria II appointed a committee to draw up an official pharmacopoeia. Consequently, a pharmacopoeia was published in 1841 called *Pharmacopoeia Lusitana*. It was never declared the official pharmacopoeia, a matter which needs further investigation.

*Pharmacopoeia Portuguesa* (Gomes et al. 1876) was the third official Portuguese pharmacopoeia, and the first to be written by a committee. This committee consisted of physicians, pharmacists, and chemists (Gomes et al. 1876 p. v-viii). It was chaired by Bernardino António Gomes (1806-1877), a leading figure of Portuguese medicine and pharmacology in the mid-19<sup>th</sup> century. This pharmacopoeia consists of almost five hundred pages of drug monographs (plant, animal, and mineral and chemical) and a long list of formulations. No distinction is made between the drugs and the formulations; they are presented sequentially and in alphabetical order. The committee found that the traditional division between *materia medica* (the monographs on drugs and pharmaceuticals) and *pharmacopoeia* (the pharmaceutical forms and the formulations) was not appropriate for this work. When it was published, *Pharmacopoeia Portuguesa* was considered a modern and innovative work. It can be considered the last official Portuguese pharmacopoeia of the pre-industrial pharmaceutical world. It was precisely in the second half of the 19<sup>th</sup> century that the industrialisation of medicines began. It should be remembered that the first large-scale Portuguese pharmaceutical industry was the Companhia Portuguesa de Higiene, founded in 1891. However, due to the scientific and technological innovations that were taking place, the pharmacopoeia went quickly out of date. Indeed, the second half of the 19<sup>th</sup> and the first quarter of the 20<sup>th</sup> century were a fertile period of pharmacotherapeutic innovations and new concepts of medicine, thanks to the industrialisation of medicines. And pharmacopoeias had to keep up to date in view of the standardisation process for the sake of private and public health. The 1876 Pharmacopoeia did not keep up with the required updates. The scientific and professional community called for its review as other countries were doing. For example, from 1884 to 1954, Spain published six official pharmacopoeias, one of which was published three times. We only need to skim some Portuguese periodical publications, namely the *Jornal da Sociedade Farmacêutica Lusitana* (Journal of the Portuguese Pharmaceutical Society), to notice the appeals that were being made for a review of the pharmacopoeia. The scientific, socio-professional, and political turmoil in Portugal at the time explains why the pharmacopoeia remained in force beyond a reasonable limit of time. Some committees appointed to review the pharmacopoeia did not complete their work: professional conflicts and the revolutionary process of the Republic (1910) caused instability in the review process and the functioning of the committees appointed. Examples include the committees appointed to draft a new pharmacopoeia in 1903 and 1913. The first, appointed by the then President of the Council, Ernesto Hintze Ribeiro, and chaired by the prestigious physician and pharmacologist Eduardo Augusto Motta, met for 7 years. Everything seems to suggest that the social unrest resulting from the republican revolution prevented the work from reaching its

conclusion. Committee members were visibly uncomfortable with the situation. The committee officially appointed in 1913 and chaired by Professor of Medicine Bello Morais was strongly opposed by several class organisations, such as the Portuguese Pharmaceutical Society. Consequently, the committee never bore fruit.

The *Farmacopoeia Portuguesa IV* (the fourth official pharmacopoeia in Portugal) was first published in 1935 (Fonseca et al. 1935). The second reviewed edition was published in 1946 (Fonseca et al. 1946). A supplement to the second edition of the *Farmacopoeia Portuguesa IV* was published in 1961 (Comissão Permanente da Farmacopoeia Portuguesa 1961). *Farmacopoeia Portuguesa IV* replaced the outdated *Pharmacopoeia Portuguesa* of 1876, which remained in force for about six decades until the fourth official Portuguese Pharmacopoeia was published in 1935. *Farmacopoeia Portuguesa IV* was written by a committee of pharmacists who made use of foreign pharmacopoeias and other works of international reference. The five committee members were connected with the pharmaceutical inspectorate or the army and navy pharmacy. It was published after the political revolution that happened on 28 May 1926, which marked the end of the First Republic and the beginning of the dictatorship regime, also known as *Estado Novo*. *Farmacopoeia Portuguesa IV* introduced several innovations in the area of drugs and medicines. The 1961 supplement was the result of the work carried out by the Comissão Permanente da Farmacopoeia Portuguesa (Portuguese Pharmacopoeia Standing Committee). This committee was created in 1955 and its members were appointed in 1957. The committee was mandated to draft and review the Portuguese Pharmacopoeia. *Farmacopoeia Portuguesa IV* was officially in force until 1986. This pharmacopoeia must be viewed in the context of legislative measures taken to standardise pharmaceutical activities in Portugal and enacted by the *Estado Novo* regime. The pharmacopoeia and its supplement paved the way for the pharmaceutical industrial world. However, due to the lack of systematic review for decades it became obsolete.

*Farmacopoeia Portuguesa V* was the fifth official Portuguese pharmacopoeia. It was drawn up by the Portuguese Pharmacopoeia Standing Committee and is already a translation-adaptation of the European Pharmacopoeia (Comissão Permanente da Farmacopoeia Portuguesa 1986). Its publication and subsequent editions are the result of Portugal's accession to the European Union and of the European Union's requirements in this area, as was the enactment in Portugal of the first Statute of Medicines in 1991. *Farmacopoeia Portuguesa V* was published in several volumes between 1986 and 1996 (Comissão Permanente da Farmacopoeia Portuguesa 1986, 1987a, 1987b, 1988a, 1988b, 1989, 1990, 1991, 1992, 1993, 1995a, 1995b, 1996) and includes a *Memento terapêutico* (Comissão Permanente da Farmacopoeia Portuguesa 1995b) which lists the medicines and their therapeutic indications, their posology and method of administration. The publication of this work paved the way for contemporary official pharmacopoeias in line with the European Pharmacopoeia, as was the case of the sixth official pharmacopoeia, *Farmacopoeia Portuguesa VI*, published in 1997 by the Portuguese Pharmacopoeia Committee (Comissão da Farmacopoeia Portuguesa 1997). The *Farmacopoeia Portuguesa VI* had 4 supplements (Comissão da Farmacopoeia Portuguesa 1998a, 1999, 2000, 2001) and is also a translation-adaptation of the European Pharmacopoeia (Comissão da Farmacopoeia Portuguesa 1997 p. XIII). The Portuguese Pharmacopoeia Committee has also published another edition of the *Memento Terapêutico* (Comissão da Farmacopoeia Portuguesa 1998b). Since 1997, the Portuguese Pharmacopoeia has been published under the full responsibility of the INFARMED-Instituto Nacional da Farmácia e do Medicamento (National Pharmacy and Medicines Institute) that reports to the Portuguese Ministry of Health.

### 3. Review of official pharmacopoeias: the importance of Cinchona bark and medicines containing quinine

In our analysis of the official Portuguese pharmacopoeias the entries were divided into two large groups: drugs of natural origin

(which include plant-derived crude drugs, animal, and mineral drugs) and medicines. The plant-derived drugs have been subdivided by geographical origin. This classification is based on the categorisation used by José Pedro Sousa Dias (Dias 1991) and João Rui Pita in their Doctoral theses (Pita 1995). The bark of the *Cinchona* tree is under the plant-derived drugs of American origin category. Preparations with *Cinchona* bark, quinine and other *Cinchona* alkaloids fall under the category of medicines. The data collected in this analysis includes number of monographs on the *Cinchona* bark plant-derived drug; number and percentage of medicines made from *Cinchona* bark; number and percentage of medicines made from quinine; and number and percentage of medicines made from other *Cinchona* alkaloids. The percentages are calculated in relation to the total number of medicines in each pharmacopoeia.

### 3.1. *Cinchona* bark in *Pharmacopeia Geral* (1794)

*Pharmacopeia Geral* (1794) incorporates two monographs on *Cinchona* bark. The monograph “Quina ou Casca peruviana” (*Cinchona* bark or Peruvian bark) (*Pharmacopeia Geral* 1794 p. 90), referred to as belonging to the species *Cinchona officinalis* Linn (Fig. 3); and the monograph “Quina vermelha” (red *Cinchona* bark) (*Pharmacopeia Geral* 1794 p. 90), species unknown. Therefore, in the first official Portuguese pharmacopoeia, only one species of the genus *Cinchona*, *Cinchona officinalis* Linn is mentioned. The categorization of *Cinchona* bark by colour was a common practice at the time. *Pharmacopeia Geral* also contains a total of 6 medicines made from *Cinchona* bark (1.92% of all medicines).

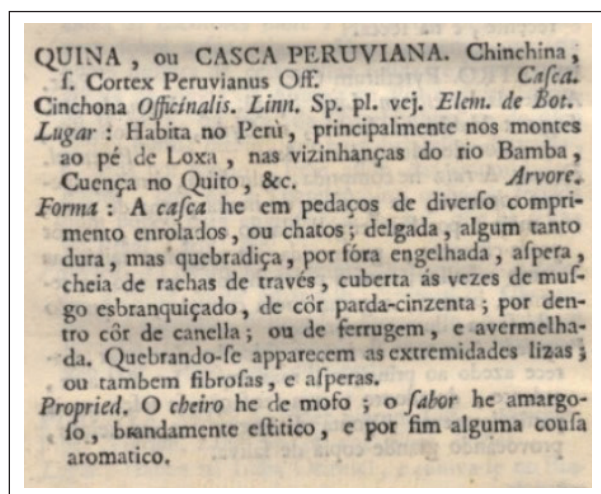


Fig. 3: *Cinchona* bark or Peruvian bark monograph in the *Pharmacopeia Geral* (1794, vol. 2, p. 90).

### 3.2. The innovations of the *Codigo Pharmaceutico Lusitano*

By analysing the *Codigo Pharmaceutico Lusitano* we found that in the 1835 edition there is no monograph on *Cinchona* bark. It should be noted, however, that this pharmacopoeia includes only one monograph on a drug derived from a plant, opium. *Codigo Pharmaceutico Lusitano* of 1835 lists 13 medicines containing *Cinchona* bark in their composition (1.80%). Quinine is present in 6 medicines (0.83%). The author highlights further that quinine sulphate was “a medicine widely used for treatment” (Pinto 1835 p. 225), a direct clue to its relevance in the medicine of that era. *Codigo Pharmaceutico Lusitano* of 1835 also contains two other entries related to *Cinchona* bark (0.28%): cinchonine and cinchonine sulphate. Cinchonine has a detailed monograph. The monograph on cinchonine describes two processes for obtaining it, both from the bark of grey *Cinchona*, and identifies the person who first isolated it (Pinto 1835 p. 74-75) in 1810, the Portuguese

physician Bernardino António Gomes (1768-1823) (Gomes 1812). In the monograph on cinchonine it is also stated that cinchonine and quinine are responsible for the antipyretic action of *Cinchona* bark: “In these two alkaloid principles lies the febrifuge property of *Cinchona* bark” (Pinto 1835 p. 75). This evidence suggests that in 1835 in Portugal, the role of quinine in medicine and therapy was growing compared to cinchonine, since it was included in a larger number of medicines. As highlighted before, *Codigo Pharmaceutico Lusitano* of 1835 does not include a monograph on *Cinchona* bark. However, in *Pharmacographia do Codigo Pharmaceutico Lusitano* (Pinto 1836a), the work commissioned by D. Maria II of Portugal that supplemented the *Codigo Pharmaceutico Lusitano*, there is a monograph on the genus *Cinchona*. The author specifies the genus and family of the plant and clarifies that it was an exotic plant whose bark was used for medicinal purposes. Furthermore, he states the common name of the *Cinchona* bark in French, English, Latin and Portuguese. He goes on saying that the *Cinchona* plant is found in Peru, on the American continent and that “Many barks are sold under this name”. The author sets out to describe *Cinchona* barks that are “best known and most common in Drugstores and workshops” (Pinto 1836a p. 194). He divides *Cinchona* bark into five types: “Quinas cinzentas, ou alaranjadas” (grey or orange *Cinchona* barks) (Pinto 1836a p. 194); “Quinas vermelhas” (red *Cinchona* barks) (Pinto 1836a p. 195); “Quinas amarellas” (yellow *Cinchona* barks) (Pinto 1836a p. 196); “Quinas brancas” (white *Cinchona* barks) (Pinto 1836a p. 197); and “Quinas falsas” (false *Cinchona* barks) (Pinto 1836a p. 198). False *Cinchona* bark was also known as “quina” (*Cinchona* bark), its Portuguese common name, but it did not contain quinine nor cinchonine. In *Pharmacographia of the Codigo Pharmaceutico Lusitano* Silveira Pinto also states that “*Cinchona* barks are the most active tonics, with antiseptic, antispasmodic, antiperiodic, and febrifuge properties in eminent degree” (Pinto 1836a p. 198).

As in the first edition, the *Codigo Pharmaceutico Lusitano* of 1836 also does not contain a monograph on *Cinchona* bark. In the 1836 edition, *Cinchona* bark is still the most represented plant-derived drug of American origin in the medicines, with 13 formulations (1.54%). It also includes 6 medicines containing quinine (0.71%) and 2 medicines with cinchonine (0.24%). The quinine monograph is more developed in this edition. It also describes one more method of obtaining quinine, instead of simply referring to the cinchonine monograph, as was the case in the first edition of *Codigo Pharmaceutico Lusitano*.

The 1841 edition of the *Codigo Pharmaceutico Lusitano* does not include a monograph on *Cinchona* bark either (and contains only one monograph on a drug derived from a plant, opium). The medicines containing quinine, cinchonine and *Cinchona* bark are the same as those listed in the first two editions of the *Codigo Pharmaceutico Lusitano* and there are no changes in the text of the monographs. The pharmacopoeia thus includes 13 medicines made from *Cinchona* bark (1.50%), 6 medicines containing quinine (0.69%) and 2 medicines that include cinchonine (0.23%).

The fourth edition of *Codigo Pharmaceutico Lusitano* (1846) also does not include a monograph on *Cinchona* bark. However, in the opening pages of *Codigo Pharmaceutico Lusitano* from 1846 *Cinchona* bark is mentioned. In the “Catalogue of Medicinal Plants that are generally used in Materia Medica, in alphabetical order, and in relation to Linneo’s sexual system, according to Sprengel in the 16th Edition” (Pinto 1846 p. XIX) it is said that the bark of *Cinchona caribaea* has tonic virtues, like the “*Quina de Piton, ou de S. Domingos*” (Piton or Saint Domingos *Cinchona* bark) of the genus *Cinchona floribunda* (Pinto 1846 p. XXIX). Additionally, the “Second Catalogue of some Brazilian plants used in Brazil for medicinal purposes; which should be part of any materia medica” (Pinto 1846 p. XXXIV) mentions *Cinchona brasiliensis* (Wildenow) commonly called *Quina do Brasil* (Brazilian *Cinchona* bark), pointing out its tonic and astringent properties; *Cinchona vellosii* and *Cinchona remigeana* (S.<sup>1</sup> Hilaire) (Pinto 1846 p. XXXVII). Currently, the species mentioned by Silveira Pinto in this pharmacopoeia are not included in the genus *Cinchona* (WFO 13 Jan. 2021). In this 1846 edition, the medicines

containing quinine, cinchonine and *Cinchona* bark are the same as those in the first three editions. Consequently, there are 13 medicines made from *Cinchona* bark (1.48% of all medicines in this edition), 6 medicines from quinine (0.68% of all medicines in this pharmacopoeia) and 2 medicines from cinchonine (0.23% of the total number of medicines). There are only nomenclatural changes for two medicines with *Cinchona* bark: “Oino-infuso de quina” is renamed “Oinoleo de quina” (Pinto 1846 p. 465), and “Oino-infuso de quina” (Pinto 1846 p. 465) is called “Oinoleo de quina composto” (Pinto 1846 p. 465).

Unlike modern pharmacopoeias in general, the first 4 editions of *Código Farmacêutico Lusitano* (editions of 1835, 1836, 1841 and 1846) provide therapeutic indications for some medicines. “Hydralcooleo de quina” (Pinto 1835 p. 30) and “alcooleo de quina composto” (Pinto 1835 p. 36) were found to have tonic properties; “decocto de quina composto” (Pinto 1835 p. 36) was advised to treat “asthenia, muscle weakness, typhus, etc.” (Pinto 1835 p. 85); “electuario de quina antimoniado” was “extremely effective in intermittent, refractory [fevers]” (Pinto 1835 p. 87) and the *Cinchona* bark compound wine was a substitute for the “medicine known as Water of England” (Pinto 1835 p. 173). Regarding medicines made from quinine and cinchonine, Silveira Pinto stated that “hydro-ferro cyanato de quinina” (a quinine salt) was good for treating “intermittent, refractory fevers” (Pinto 1835 p. 140); quinine sulphate was deemed “eminent in intermittent fevers” (Pinto 1835 p. 224) and was advised by *Klo-kow* “also in passive haemorrhages” (Pinto 1835 p. 224); and cinchonine and quinine possessed febrifuge properties.

The fifth edition of *Código Farmacêutico Lusitano* (published in 1858 after Silveira Pinto died and edited by José Pereira Reis) does not include a monograph on *Cinchona* bark either. However, this does not mean that *Cinchona* bark was not deemed important, since this pharmacopoeia does not include any monograph on plant, mineral, or animal-derived drugs. *Cinchona* bark is still the plant-derived drug of American origin with most entries, 29 in total (2.29%). In this edition of *Código Farmacêutico Lusitano* there is generally no information on therapeutic indications, contrary to the first 4 editions, in which the medicines described often provided therapeutic indications and/or dose recommendations. Nonetheless, the names themselves of some medicines are indicative of their therapeutic action. For example, “Decocto de quina composto”, also called “*Cosimento antifebril*” (Pinto 1858 p. 212) suggests it was used to treat fever (*antifebril* means febrifuge in Portuguese); or “Alcooleo de quina composto”, also called “*Essência antisséptica ou alexifármaca* de Huxham” (Pinto 1858 p. 165), which points to its action as an antiseptic or counterpoison agent. There are still less medicines containing quinine (11) registered in this pharmacopoeia (0.87% of the total) than the medicines containing *Cinchona* bark. Quinine is the only *Cinchona* bark alkaloid mentioned in this edition of *Código Farmacêutico Lusitano*. Cinchonine’s absence suggests that it was not approved for therapeutic use in Portugal in 1858. There are more medicines containing quinine compared to Silveira Pinto’s editions (from 6 in the editions penned by Silveira Pinto to 11 in the 1858 edition). One of the medicines, “Enema de quinina” (quinine enema) is also called “*Clister febrífugo*” (febrifuge enema) (Pinto 1858 p. 232), so one can infer that it was used to treat fever.

### 3.3. *Pharmacopêa Portuguesa* (1876) and expanding the drug arsenal

The only monograph on the *Cinchona* bark in *Pharmacopêa Portuguesa* describes three varieties of *Cinchona* bark: yellow, “From the *Cinchona Calisaya* Weddel” (Gomes et al. 1876 p. 348); grey, “From the *Cinchona micrantha* Ruiz and Pavon, from *Cinchona nitida* Ruiz and Pavon, from *Cinchona Urituzinga* Pavon and other similar species” (Gomes et al. 1876 p. 348); and red, “From *Cinchona succirubra* Pavon” (Gomes et al. 1876 p. 349). Additionally, this pharmacopoeia sets quality standards for these barks based on the percentage of quinine. The monograph on the *Cinchona* bark also lays down the method for determining the

quinine content. It points out further that “where there is no indication in particular” (Gomes et al. 1876 p. 349), yellow *Cinchona* bark (the bark with the highest minimum acceptable quinine content) should be used. *Pharmacopêa Portuguesa* includes 21 medicinal products made from *Cinchona* bark (2.61%). There are also 9 medicines containing quinine (1.12%) (Fig. 4) and 2 with cinchonine (corresponding to 0.25% of the medicines in the third official Portuguese pharmacopoeia). Interestingly this pharmacopoeia, published in 1876, still included many preparations containing *Cinchona* bark. Quinine had already been isolated in 1820 and provided proof of action in the treatment of intermittent fevers. Furthermore, the use of an isolated substance such as quinine made it possible to effectively dose and standardise the doses administered, and consequently to obtain more reproducible therapeutic results. However, observing the quantity of medicines made from *Cinchona* bark listed in *Pharmacopêa Portuguesa* of 1876, it can be inferred that medicinal products made from *Cinchona* bark were still administered in Portugal. Such evidence therefore suggests that, in Portugal, quinine did not readily replace *Cinchona* bark in therapeutics. One of the possible reasons for medicines containing *Cinchona* bark lasting this long in Portugal was the high price of quinine, which Silveira Pinto alluded to in the first four editions of *Código Farmacêutico Lusitano* (Pinto 1835 p. 225-226; Pinto 1836 p. 451; Pinto 1841 p. 579; Pinto 1846 p. 528). On the other hand, the possible mistrust about a new product, although extracted from a well-known and appreciated drug such as *Cinchona* bark, may also have resulted in the persistent direct use of *Cinchona* bark in medicines.

TINCTURA DE SULFATO DE QUININA.	
<i>Tinctura Sulfatis quinini.</i>	
ALCOOLITO DE SULFATO DE QUININA. ALCOOLEO DE SULFATO DE QUININA.	
Sulfato de quinina . . . . . dez grammas	10
Alcool a 85° . . . . . novecentos e noventa grammas	990
Dissolva; filtre.	

Fig. 4: Monograph of a medicine containing quinine sulfate – “Tinctura de sulfato de quinina” (Quinine sulfate tincture) – described in the *Pharmacopêa Portuguesa* (1876, p. 432), the third Portuguese official pharmacopoeia.

As is the case today, *Pharmacopêa Portuguesa* does not contain therapeutic indications for the medicines or drugs of natural origin it describes. However, some medicines are still called by their alternative name that indicates their therapeutic action. Quinine sulphate, for example, was also called “*Sal anti-periodico*” (anti-periodic salt) or “*Sal febrifugo*” (febrifuge salt) (Gomes et al. 1876 p. 396) suggesting it was good for treating fever (namely of an intermittent nature) and other periodic diseases.

### 3.4. *Farmacopêa Portuguesa IV* (1935, 1946) and its supplement (1961): the modernisation of drug standardisation

*Farmacopêa Portuguesa IV* of 1935 includes a monograph on *Cinchona* bark (Fonseca et al. 1935 p. 433-434). There are two “types” of *Cinchona* bark described in this monograph: yellow *Cinchona* bark, also called “quina calisaia” (calisaya *Cinchona* bark) or “quina real” (royal *Cinchona* bark), “Drawn from the *Cinchona Calisaya* WEDDEL, a tree from Bolivia and the province of Carabaia in Peru”; and the red *Cinchona* bark or “Quina do chimborazo” (Chimborazo *Cinchona* bark), “drawn from the *Cinchona succirubra* PAVON, a tree from Chimborazo, in New Granada” (Fonseca et al. 1935 p. 433). It also specifies the

minimum total alkaloid content and quinine content for each “type” of *Cinchona* bark (yellow and red). Yellow *Cinchona* bark should have a higher quinine content than red *Cinchona* bark (at least 2% for yellow and 1.5% for red *Cinchona* bark). The monograph on the *Cinchona* bark also describes the method for determining the total alkaloid content and the quinine content in *Cinchona* bark powder. Contrastingly, the *Pharmacopêa Portuguesa* of 1876 had only described one method for quinine content determination. The method for determination of quinine content is different from that indicated in *Pharmacopêa Portuguesa*. The note that “Where there is no indication” yellow *Cinchona* bark should be used is also kept (Fonseca et al. 1935 p. 434). *Cinchona* bark is used in the composition of 10 medicines (1.37%). Concerning *Cinchona* bark alkaloids, this pharmacopoeia contains 17 medicines that incorporate quinine (2.34% of all medicines) - two of them injectable - and one medicine with quinidine, quinidine sulphate (0.14% of the medicines). Quinine sulphate is also called antiperiodic salt, again alluding to its properties for the treatment of periodic diseases (Fonseca et al. 1935 p. 496).

It should be noted that quinidine is only included in the official Portuguese Pharmacopoeia in 1935, in the form of a salt, quinidine sulphate, although it had already been isolated in 1833 by Henry and Delondre (Henry and Delondre 1833, 1834). However, there is no monograph dedicated to the active ingredient quinidine. The same applies to quinine, which does not have a monograph dedicated to it.

The medicines containing quinine have almost doubled compared to the number in the previous pharmacopoeia (from 9 to 17). The proportion of medicines containing quinine also increased (from 1.12% to 2.34%). This increase in the number and percentage of quinine-containing medicines suggests a growing importance of quinine in therapeutics. Furthermore, the pharmacopoeia introduces 10 medicines prepared directly with *Cinchona* bark, which is congruent with a still frequent therapeutic use of *Cinchona* bark preparations in Portugal. The drafting committee of this pharmacopoeia reports further that “it is well known that quinine is the most important and the most precious medicine” extracted from *Cinchona* bark (Fonseca et al. 1935 p. XI).

In the second revised edition of *Farmacopeia Portuguesa IV* (1946) there is also a monograph on *Cinchona* bark. Compared to the 1935 edition, the *Cinchona* bark monograph has more information on where *Cinchona* trees are grown, indicating that they are cultivated: “on the island of S. Tomé, in India and above all in the Dutch colonies of the East” (Fonseca et al. 1946 p. 454). The method of determination of total alkaloid content in *Cinchona* bark is maintained, but the method for determining the quinine content is different from that presented in the 1935 edition (Fonseca et al. 1946 p. 455-456). The monograph on the *Cinchona* bark also specifies that “Where there is no indication” yellow *Cinchona* bark must be used (Fonseca et al. 1946 p. 456).

The medicines made from the bark of the *Cinchona* tree are the same as in the 1935 edition (a total of 10, which corresponds to 1.20% of all medicines). There are 19 medicines containing quinine (2.29%), two of which were not mentioned in the 1935 edition: quinine sulphate tablets (monograph in the 1961 supplement) and totaquine, a mixture of alkaloids extracted from *Cinchona* bark. There is also a monograph on quinidine sulphate (0.12% of all medicines). Quinine sulphate is still called antiperiodic salt, indirectly alluding to its therapeutic properties.

### 3.5. *Farmacopeia Portuguesa V (1986-1996) and Memento terapêutico (1995): under European standards*

*Farmacopeia Portuguesa V* includes a monograph on *Cinchona* bark. The monograph provides a definition for *Cinchona* bark, specifying the minimum total alkaloid content and the relative minimum and maximum quinine-type alkaloid content. *Cinchona* bark’s macroscopic and microscopic characters are described, as well as its identification tests and the method of determination of total alkaloid content and the relative quinine-type alkaloid content. It also provides advice on how to store this plant-derived drug and

specifies the reagents that are used to assess the *Cinchona* bark samples. The fifth official Portuguese pharmacopoeia contains 3 medicines with quinine (0.28% of all medicines) and 1 medicine with quinidine (0.09%).

*Memento Terapêutico* has 3 entries on *Cinchona* bark: hydroquinidine (hydrochloride), a quinidine derivative used as an antiarrhythmic agent; quinidine (sulphate, bisulphate and polygalacturonate), antiarrhythmic agent as well; and quinine (sulphate), defined as an antimalarial substance used to prevent and treat malaria caused by *Plasmodium falciparum* (routes of administration: oral and intravenous). The proportion of quinine-containing medicines in *Memento Terapêutico* is 0.18%, and medicines containing other *Cinchona* bark alkaloids account for 0.36% (Comissão Permanente da Farmacopeia Portuguesa, 1995b).

### 3.6. *Farmacopeia Portuguesa VI (1997), its Supplements (1998, 1999, 2000, 2001) and Memento terapêutico (1998): the consolidation of the European influence*

The data below are drawn from the compilation of the monographs in *Farmacopeia Portuguesa VI* (1997) and its Supplements of 1998, 1999, 2000 and 2001.

The pharmacopoeia contains a monograph on *Cinchona* bark. The monograph on the drug “Quina, Casca” (bark of the *Cinchona* tree) (Comissão da Farmacopeia Portuguesa 1997 p. 1380) is divided into 6 sections: definition; characteristics; identification (it explains how we can make sure that the sample is indeed *Cinchona* bark); assay, where the required tests for a *Cinchona* bark sample are described: “Foreign elements”, “Total ash”, “Hydrochloric acid insoluble ash”; dosage (which describes how to determine “percentage of quinine-type alkaloid content”, “percentage of cinchonine-type alkaloid content”, “total alkaloid content” and “relative quinine-type alkaloid content”); and preservation (Comissão da Farmacopeia Portuguesa 1997 p. 1381). There are 3 medicines containing quinine in this pharmacopoeia (0.20%). And a medicine containing quinidine (0.07% of medicines).

The 2<sup>nd</sup> edition of *Memento Terapêutico* (1998) has 3 entries on *Cinchona* bark: hydroquinidine (hydrochloride); quinidine (sulphate, bisulphate and polygalacturonate); and quinine (sulphate or hydrochloride). The therapeutic indications are the same as in *Memento Terapêutico* of 1995. The medicines hydroquinidine (hydrochloride) and quinidine (sulphate, bisulphate and polygalacturonate) were recommended as antiarrhythmic agents; and quinine (sulphate or hydrochloride) was recommended to treat or prevent malaria. The quinine-containing medicines in *Memento Terapêutico* (Comissão da Farmacopeia Portuguesa 1998b) account for 0.06% of all medicines therein and medicines with other *Cinchona* bark alkaloids account for 0.11%.

## 4. Discussion

The official Portuguese pharmacopoeias contain the medicines officially approved for therapeutic use. Since the official pharmacopoeias were adopted by the Portuguese government, this quantification allows us to infer the theoretical importance of *Cinchona* bark and quinine’s role in pharmacotherapy in Portugal. Nevertheless, an official pharmacopoeia may include only one medicine containing quinine or *Cinchona* bark, which is frequently prescribed and used. On the other hand, a medicine rarely used in therapy may be approved. Consequently, this analysis only points out which medicines containing *Cinchona* bark or *Cinchona* bark alkaloids were approved in Portugal in the period studied (1794–2001) and does not indicate how frequently they were prescribed or advised by physicians or self-medicated. However, more medicines containing *Cinchona* bark and/or quinine suggest a greater importance of *Cinchona* bark and quinine in medicine and therapeutics.

The analysis of the pharmacopoeias highlights variation in the amounts and proportions of medicines made from *Cinchona* bark and quinine in the official Portuguese pharmacopoeias (Fig. 5).

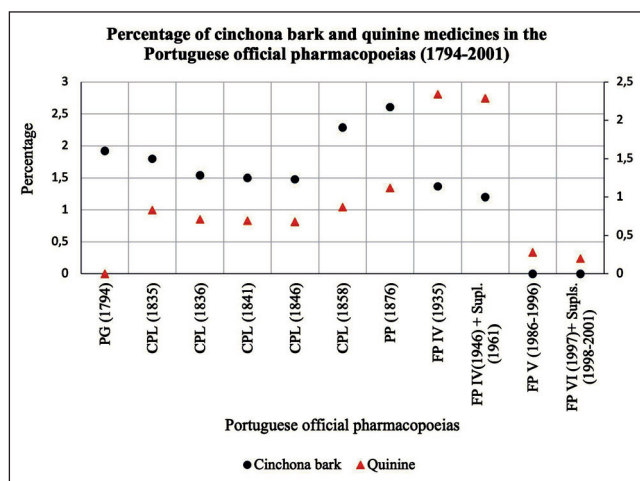


Fig. 5: Percentage of medicines made from cinchona bark and quinine in the Portuguese official pharmacopoeias (1794-2001). Abbreviations: PG – *Pharmacopoeia Geral*; CPL – *Código Pharmaceutico Lusitano*; PP – *Pharmacopêa Portuguesa*; FP IV – *Farmacopoeia Portuguesa IV*; Supl. – Supplement for the 2nd edition of the *Farmacopoeia Portuguesa IV*; FP V – *Farmacopoeia Portuguesa V*; FP VI – *Farmacopoeia Portuguesa VI*; Supls. – Supplements for the *Farmacopoeia Portuguesa VI*. Based on data collected in the analysis of Portuguese official pharmacopoeias published from 1794 to 2001.

The first official Portuguese pharmacopoeia (published in 1794) does not include any medicines containing quinine (which is to be expected considering that quinine was only isolated in 1820) and there are 6 medicines prepared with *Cinchona* bark. However, in the last two official Portuguese pharmacopoeias analysed (*Farmacopoeia Portuguesa V* and *Farmacopoeia Portuguesa VI*) there are 3 medicines containing quinine and no medication containing *Cinchona* bark. In *Farmacopoeia Portuguesa V* and *Farmacopoeia Portuguesa VI*, *Cinchona* bark is listed only as a plant-derived drug. However, the official Portuguese pharmacopoeia of 1946 still included 10 medicines containing *Cinchona* bark. Formulations containing *Cinchona* bark were most certainly prepared in pharmacies and/or hospitals, which justifies the inclusion of medicines containing *Cinchona* bark in the official Portuguese pharmacopoeia.

The official Portuguese pharmacopoeia with the highest proportion of medicines containing *Cinchona* bark is *Pharmacopêa Portuguesa* (2.61%), with a total of 21 medicines made from the bark of the *Cinchona* tree.

The first edition of *Farmacopoeia Portuguesa IV* (1935) is the official pharmacopoeia with the highest percentage of quinine-containing medicines (2.34%).

Quinine is mentioned since 1835, in *Código Pharmaceutico Lusitano*. In the first four editions of *Código Pharmaceutico Lusitano*, only 6 medicines containing quinine were listed. The number fluctuated throughout the following official pharmacopoeias up to the absolute maximum of 19 quinine-containing medicines in the second edition of *Farmacopoeia Portuguesa IV* (1946) (although the 1935 edition of *Farmacopoeia Portuguesa IV* has the highest proportion of medicines containing quinine). In the last two official Portuguese pharmacopoeias the number of medicines containing quinine decreased to 3, and the percentage of quinine-containing medicines also decreased.

Another *Cinchona* bark alkaloid used for therapeutic purposes, quinidine (used namely as an antiarrhythmic agent), was isolated in 1833, but only appears in the official Portuguese pharmacopoeia published in 1935, in the form of quinidine sulphate. The official Portuguese pharmacopoeias that followed (the second edition of *Farmacopoeia Portuguesa IV*, *Farmacopoeia Portuguesa V* and *Farmacopoeia Portuguesa VI*) still include a monograph on quinidine sulphate, which suggests that this medicine derived from *Cinchona* bark was still used.

Cinchonine appears for the first time in official Portuguese pharmacopoeias in *Código Pharmaceutico Lusitano* of 1835, remaining

on the list of medicines until the fourth edition of *Código Pharmaceutico Lusitano* (1846). The fifth edition of *Código Pharmaceutico Lusitano* (1858) does not have a cinchonine monograph, but it appears again in the third official Portuguese Pharmacopoeia (*Pharmacopêa Portuguesa* of 1876). *Farmacopoeia Portuguesa IV* (1935, 1946 and the 1961 Supplement) does not include a monograph on cinchonine. In *Farmacopoeia Portuguesa V* and *Farmacopoeia Portuguesa VI* cinchonine is listed under the reagents alone. Across the pharmacopoeias analysed, the monographs on *Cinchona* bark and quinine-containing medicinal products grow in complexity and in the quality specifications considered. *Pharmacopêa Portuguesa* specifies for the first time the minimum required quinine content in *Cinchona* bark for it to be suitable for therapeutic use, suggesting a growing need for laboratory quantification to guarantee the quality of the medicines.

*Código Pharmaceutico Lusitano* endorses the use of *Cinchona* bark for the treatment of intermittent fevers, recommends it as a tonic and for the treatment of “passive haemorrhage”. Other pharmacopoeias do not directly mention the therapeutic uses of *Cinchona* bark and quinine, but *Pharmacopêa Portuguesa* and *Farmacopoeia Portuguesa IV* (in both the 1935 and 1946 editions) include alternative designations for quinine sulphate which are suggestive of its therapeutic use. The *Memento Terapêutico de Farmacopoeia Portuguesa V* and *Farmacopoeia Portuguesa VI* underscores the antimalarial activity of quinine.

From *Pharmacopoeia Geral* (1794) to *Pharmacopêa Portuguesa* (1876) the proportion of medicines containing *Cinchona* bark is higher than that of medicines with quinine. In *Farmacopoeia Portuguesa IV* (1935), the percentage of quinine-containing medicines is higher than that of medicines containing *Cinchona* bark, a trend which continued until *Farmacopoeia Portuguesa VI*. This evidence suggests that the bark of the *Cinchona* tree gradually gave way to quinine in therapy.

## 5. Conclusion

The results of this first broad quantitative study of the presence of *Cinchona* bark and quinine in official Portuguese pharmacopoeias hint at the important role that the two played in therapeutics. *Cinchona* bark is included in all the official Portuguese pharmacopoeias analysed (1794-2001). Quinine, on the other hand, has been present since the second official Portuguese pharmacopoeia (1835). *Cinchona* bark and quinine thus have a remarkable longevity as officially recognised therapeutic agents. Nevertheless, one must look further into medical and pharmaceutical literature, and actual prescription and consumption of *Cinchona* bark and quinine for a more holistic view of its role in therapeutics in Portugal.

Conflicts of interest: None declared.

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