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Bitter plants used as substitute of *Cinchona* spp. (quina) in Brazilian traditional medicine

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ABSTRACT

Ethnopharmacological relevance: Bitter tasting plant species are used as tonics and have been previously used to treat intermittent fevers in Brazil, the principal symptom of malaria. Many of these species were named quina and were used as substitutes of *Cinchona* spp., the source of quinine.
Aim of the study: To present data on these bitter species named quina and to discuss their potential as sources of bioactive substances.
Materials and methods: Data about the plants were obtained from a survey of the literature and documents written by early naturalists and clinical doctors living in the 18th and 19th centuries in Brazil. Correlated pharmacological studies were obtained from different scientific databases.
Results: A total of 29 species were recorded. The largest number of species belonged to the Rubiaceae family (14), being *Remijia ferruginea* (A. St.-Hil) DC. the most representative. *Strychnos pseudoquina* A. St.-Hil. (Loganiaceae), *Hortia brasiliana* Vand. ex DC. (Rutaceae) and *Solanum pseudoquina* A. St.-Hil. (Solanaceae) were also frequently mentioned in the historical bibliography. Pharmacological studies have shown the presence of bitter bioactive substances useful to treat digestive disorders and/or with antimalarial activities, in all of the recorded botanic families.
Conclusion: This study shows that several bitter species named quina were used in the past as substitute of *Cinchona* spp. and studying these plants can lead to the development of new products.

1. Introduction

Since 2002, the World Health Organization (WHO) has been encouraging studies with old remedies used in traditional medicine, because their secular use could confirm their efficacy as medicine (Bagla, 2011; WHO, 2011). The Brazilian flora represents one important source of such plants, due to its biodiversity, used by the Amerindians. Currently, however, despite medicinal plants being widely used in Brazil by both rural and urban populations, the mainly known and used species are native from other continents, and were introduced here since the beginning of the European colonization. This phenomenon is related to the mixture of cultures, but is also, and mainly, a result of the continuous destruction of the rich Brazilian ecosystems. Following the WHO orientations, our research group is focused on acquiring information and samples from plant remedies that were historically used in Brazilian traditional medicine. Data and images of the plants are constantly recovered from historical bibliography and documents prepared by naturalists, researchers and clinical doctors that lived in Brazil in the 18th and 19th centuries. These informations are important because, at that time, the Brazilian vegetation was conserved and native species were predominantly used in traditional medicine (Brandão et al., 2008, 2012; Oliveira et al., 2012; Breitbach et al., 2013).

Among the useful Brazilian plants recorded in the historical literature, several species possess a bitter taste and were used as substitute of *Cinchona* spp, known as quinas (or china). The bitter taste of the bark of *Cinchona* spp. was one of most important characteristics to consider its use as a tonic. Quinine, alkaloid present predominantly in the barks of *Cinchona calisaya* Wedd. and *Cinchona succirubra* Pav. ex Klotzsch is very bitter, and is responsible for the antimalarial activity of the quina barks. Currently, besides being used for production of antimalarials, quinine is commercially explored as ingredient of the beverage known as tonic water. Other important Amerindian bitter specie is

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Quassia amara (Simarubaceae). In the 19th century tonic-cups, prepared using the wood of this species, were very popular in North America and Canada (Odonne et al., 2007). This plant also shows strong antimalarial activity, both *in vitro* and *in vivo*, and this activity is attributed to the presence of the quassinoids, very bitter substances (Bertani et al., 2005; Cachet et al., 2009).

Other species, from different botanical families, were named quina and used as substitutes of *Cinchona* spp., as tonic and febrifuge, in the Brazilian traditional medicine. In this study, we present data on these species and discuss their potential as source of bioactive substances.

2. Materials and methods

2.1. Ethnopharmacological historical literature survey

Data about the use of the bitter species named quina were obtained from books and other documents (manuscripts) written by naturalists and clinical doctors who lived in Brazil in the 18th and 19th centuries. The book *Quinographia portugueza, ou coleção de várias memórias de 22 espécies de quinas tendentes ao seu descobrimento nos vários domínios do Brazil* (Quinographia Portuguese, or collection of several memories of 22 species of quina aiming to their discovery in the various fields of Brazil), was written in 1799 by the Brazilian naturalist Frei M.C. Vellozo. Data were also found in books (travel diaries) from European naturalists who traveled throughout Brazil in the 19th century. The diaries of the Austrian Pohl (1976), the Germans G.H. von Langsdorff (Silva, 1997) and Spix and von Martius (1981), the Englishmen Mawe (1978), Bunbury (1981) and Burton (1976, 1977), and the French Saint-Hilaire, 1975a, 1975b, 1975c, 1975d) were studied (www.dataplamt.org.br). The books specifically written about Brazilian useful plants, *Systema Materiae Medicae Vegetabilis Brasiliensis* (Von Martius, 1843), *Plantes Usuelles des Brasiliens* (Saint-Hilaire, 1842a, 1842b) and *Histoire des plantes les plus remarquables du Brésil et du Paraguay* (Saint-Hilaire, 1842a, 1842b) were carefully studied. Data were also obtained from the travel notebook (manuscripts) of Saint-Hilaire [manuscript, 1816–1822] (Brandão et al., 2012), as well as a manuscript from John Miers, (deposited in the Natural History Museum of London).

Other studied books were written by clinical doctors who worked in Brazil during the 19th century and incorporated the native medicinal species into their practices. Chernoviz (1842) was born in Poland, studied medicine in Montpellier, France, and came to Brazil in 1837. He wrote one of the most important books, *Dicionário e Guia Médico* (Dictionary and Medical Guide). This book was widely used by Doctors and Pharmacists in Brazil, until the publication of Brazilian Official Pharmacopoeia, in 1929. The Danish T. Langgaard (1813–1883) came to Brazil in 1842 and wrote the book *Dicionário de Medicina Popular e Doméstica* (Dictionary of Domestic and Popular Medicine) (Langgaard, 1865). M.A. Câmara was born in Pernambuco, Brazil, and studied medicine in Montpellier. The book *Dicionário de Botânica ou Compêndio dos Vegetais do Brasil, tanto indígenas quanto aclimatados* (Dictionary of Botany or Compendium on plants of Brazil, indigenous and acclimatized) was organized by Pinto (1873), but most of the data about the plants were described by Câmara. J.M. Caminhoá was born in Bahia, Brazil, and was a professor of medical botany at the Medicine School in Rio de Janeiro. His book, *Elementos de Botânica Geral e Médica* (Elements of General and Medical Botany) was published in 1877, and also contains data on several native plants.

It is important to emphasize that several species are described in the literature as being bitter and useful as tonic and febrifuge, but in the present study, only those named quina were recorded.

2.2. Survey on other bibliography and databases

Other data about the recorded species were searched in the following documents: A Monografia das falsas-quinas brasileiras (Monograph on Brazilian false-quine), written in 1916 by the researcher W. Peckolt (marked as 1 in Table 1); the first edition of the Brazilian Official Pharmacopoeia (1929) (Brandão et al., 2009), marked as 2 in Table 1; data on the use of the plants to prepare medicine by Brazilian Pharmaceutical Laboratories, marked as 3 in Table 1. Data on the actual use of the recorded plants was obtained from ethnobotanical studies performed specifically on antimalarial plants (Brandão et al., 1992; Milliken, 1997a, 1997b; Oliveira et al., 2003, marked as 4 in Table 1).

Results on pharmacological studies correlated with the plants used as tonic and febrifuge were verified using the scientific databases Pubmed and Scopus. The actual botanical names of each species were checked using the websites www.theplantlist.org and www.mobot.org. The status of each species as a native Brazilian plant was verified using an official Brazilian species list, *Lista de Espécies da Flora do Brasil* (http://floradobrasil.jbrj.gov.br).

3. Results

The survey of the historical documents showed the occurrence of 29 bitter plants named quina, which were used as substitutes for *Cinchona* species in Brazil in 18th and 19th centuries. The species and their families are listed in Table 1, which also includes their popular names (correlated with the name quina), the authors who cited them and results of pharmacological studies.

Among the naturalists, Von Martius (1843) described most of the species: 22 were registered in his book *Systema de Materia Medica* being seven in a special chapter about bitter remedies: *Baccharis genistelloides* sbsp. *crispa* (Spreng.) Joch. Müll., *Strychnos pseudoquina* A. St.-Hil., *Esenbeckia febrifuga* (A. St.-Hil.) A. Juss. Ex Mart., *Hortia brasiliana* Vand. Ex DC., *Discaria febrifuga* Mart., *Cestrum euanthes* Schldl. and *Solanum pseudoquina*. Vellozo described organoleptic and morphological characteristics of the bark of 19 *Cinchona* species occurring in Peru, the Caribbean and other parts of northern South America. However, the search of the online official Brazilian species list (www.floradobrasil.org.br) revealed that five of these *Cinchona* species (*Cinchona lutescens, Cinchona fusca, Cinchona bergeniana, Cinchona lambertiana* and *Cinchona cujabensis*) are native to Brazil and, actually, belong to other genera of Rubiaceae (Table 1). Vellozo also described *Solanum* sp. (quina-do-Piauhy), *Portlandia hexandra* (*Coutarea hexandra*, quina de Pernambuco) and *Coutinia illustris* (*Aspidosperma illustris* (Vell.) Kuhlm & Pirajá, quina-de-camamu). Saint-Hilaire recorded the use of 11 species, and was responsible for the botanical description of eight of them: *Strychnos pseudoquina* A. St.-Hil., *Polyouratea hexasperma* A. St.-Hil., *Remijia ferruginea* A. St.-Hil., *Remijia vellozii* (A. St.-Hil.) DC., *Bathysa australe* A. St.-Hil., *Bathysa cuspidatum* A. St.-Hil., *Esenbeckia febrifuga* A. St.-Hil. (Rutaceae) and *Solanum pseudoquina* A. St.-Hil. All of these species were published in his book *Plantes usuelles des Brasiliens* (Saint-Hilaire, 1842a, 1842b). The use of *Galipea jasminiflora* (A. St.-Hil.) Engl. (=*Ticorea febrifuga* A. St.-Hil.) as a substitute for quina, was mentioned by Saint-Hilaire several times in his travel notebook (Brandão et al., 2012). The manuscript of John Miers described eight species of quina, and the use of *Cheiloclinium cognatum* (Miers) A.C.Sm (Celastraceae) and *Quiina guianensis* Aubl. (Ochnaceae) was registered only by this author.

Among the clinical doctors, Langgaard (1865) described more species (13), followed by Câmara (Pinto, 1873), who mentioned the use of 12 species. Notably, Langaaard distributed the species in his book into three categories: (i) those belonging to genus *Cinchona*,