# PLANTS AGAINST MALARIA
## PART 1: CINCHONA OR THE PERUVIAN BARK

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One of the most compelling sagas in the history of medicine and therapeutics is the emergence of the Peruvian bark (Cinchona) and also of the pharmacologically active substance derived from it, quinine. Its discovery involved exploration, exploitation and secrecy, and it came, in the nineteenth century, to reflect the struggles of the major European powers for domination, territory and profit. This short history shows how the use of Cinchona enabled the exploration of dangerous malarial areas and in this way facilitated imperial expansion by the Western powers.

### THE PERUVIAN; JESUIT'S OR CARDINAL'S BARK

Many physicians are familiar with the story of the Countess of Chinchón, wife of the Viceroy of Peru; it was claimed by Bado that she was cured of a certain ague by Cinchona bark sometime in the late 1620s or early 1630s.[1] As with many other good stories this one is almost certainly a myth! The more likely story is that it was her husband, the Viceroy, who suffered from the ague. The Amerindians had tried the bark as a remedy to suppress shivering and, by extension, they came to use it in all sorts of febrile conditions (or agues).

The first definite written account of the medicinal properties of the bark appears to be that by Fray Antonio de1a Calancha, an Augustinian missionary who, in 1633, wrote an account of 'the fever tree' which 'grows in Loja, Peru, the bark of which when made into a powder and given as a beverage cures the tertian fevers'. He also describes its widespread use in Lima, the capital of Peru.[2]

The Jesuits (missionaries of the Society of Jesus, S. J.) now take a prominent part. In 1630, Juan Lopez, a missionary Jesuit, learned of the bark from Pedro Leiva, chieftain of the Malacatos tribe. He, and probably other Jesuits, took the knowledge of the bark back to their headquarters, St Paul's at Lima, then the central college of the order in Peru.

How did the bark get from Peru to Europe? This is a hotly disputed question but it seems likely that several of the Jesuit priests brought the bark back to Europe and introduced it to Spain (via Seville) and to Italy (via Rome). Two of the most likely candidates, both travelling in 1632, were Fathers Venegas and Messia.[3] It is difficult to be certain about the persons (and dates) as the Jesuits had all the attributes of a secret society: they communicated with each other in a secret code and also were prepared to use their knowledge of the bark to aid their struggles for power within the Church!

An important ecclesiastical figure, Cardinal de Lugo, now emerges to take the initiative in the history of Cinchona (Figure 1). De Lugo was born in Madrid in 1585 but spent his early years in Seville where he later became a Jesuit priest.[4] In 1621 he was transferred to the Collegium Romanum in Rome, then the leading educational institution of the Jesuits. He taught there with distinction from his arrival until 1643. Initially de Lugo probably obtained the Peruvian bark from Father Tafur S.J. and, impressed by his preliminary trials of its efficacy, he purchased large amounts of it at his own expense. Sturmius, a contemporary, reported that de Lugo 'gave it gratis to the fevered poor, on condition only, that they did not sell it and that they presented a physician's statement about the illness'.

**FIGURE 1**
**Cardinal de Lugo, S.J.**

The bark was distributed to patients at the Ospedale di Santo Spirito by the Cardinal (Figure 2). Puccerini, the keeper of the apothecary's shop at the Collegium Romanum, also treated many hundreds of patients a year and reported the bark to be very successful, in particular in tertian and quartan agues. As a result of this marked success, church couriers spread the word (and the bark) to Naples, Genoa, Milan, Piedmont, England, Flanders and Germany.[5] Spain had received the bark directly from Peru. In return Cardinal de Lugo received a large collection of testimonial letters and the plant became

**FIGURE 2**
**The Cardinal dispensing Peruvian bark at the Hospital Santo Spirito in Rome.**

known also as the *pulvis cardinalis* (Cardinal's powder), *pulvis de Lugo* or Cardinal's bark.[6]

In the seventeenth century, Rome was a malarious area and many cardinals died of a 'malignant ague' when attending papal congregations in the Eternal City. By the time of the Conclave of 1655, at which Alexander VII was elected as Pope, the bark was available and the 'malignant ague' (or malaria) was not recorded among the attendees. Cardinal de Lugo died in 1660. Redi wrote some years later to the noted Jesuit Chircher that 'the whole World owes a debt of gratitude to those Fathers of your most venerable Order who were the very first, much to their glory, to bring the bark to Europe'. We would now add 'and in particular to de Lugo and Puccerini'.[7]

**OLIVER CROMWELL AND THE ENGLISH CONNECTION**

Unfortunately the Protestant north of Europe regarded the Jesuit's bark (or Cardinal's bark) as a Popish remedy and treated it either with grave suspicion or with outright condemnation. Oliver Cromwell had a number of illnesses throughout his life and is said to have refused the Peruvian bark in 1658, the year of his death 'because it was a Popish remedy'. There is in fact no evidence for this apocryphal story![8] It is known that he suffered from a 'bastard tertian fever' for some years but whether this was due to malaria or chronic pyelonephritis secondary to renal calculi (as Bruce-Chwatt has suggested) cannot now be established.[9] It has even been asserted that Cromwell was poisoned by Royalists.[10]

The bark probably arrived in England from Belgium or Holland. The first definite mention of its use was by John Metford of Northampton in 1656, who reported that he had cured a pregnant woman of a quartan fever by giving her small doses of the bark. Unfortunately, at about the same time, a London alderman called Underwood died after taking what appears to have been an overdose of the medication. The distinguished physician Sydenham initially condemned the cure but later, as a result of the work of Talbor, was forced to change his mind!

Robert Talbor (or Tabor) would rediscover the importance of administering the correct dose of the bark, a fact that had been well known to de Lugo and Puccerini 40 years earlier, and would popularise this so-called English remedy. Talbor was born in the cathedral city of Ely in the English Fens in the year 1642.[11] The Fens were a low lying swampy area not yet drained by the Dutch engineers and as a result the inhabitants were subject to severe tertian and quartan agues which caused a great deal of misery, and sometimes death. Talbor resolved to tackle this problem and the opportunity arose when he was apprenticed as a trainee apothecary to a Mr Dent in Cambridge.

Talbor learned during his apprenticeship of the Jesuit's bark (Devil's powder to Protestants!) and resolved to carry out further work on the substance, as he said later, 'in that good old fashioned way – observation and experiment'. He left his apprenticeship, moved to a marshy and malarious area of Essex and began a long series of experiments on the Peruvian bark. He kept his experiments and results to himself as he intended to reap some pecuniary advantage. As we shall see, he succeeded very well in this objective. During the course of the 1660s he was able to develop a formulation of the bark which proved very successful in curing the 'Essex ague.' Dobson has suggested recently that this was probably caused by either *Plasmodium malariae* (or *P. vivax*) transmitted by the mosquito *Anopheles atroparvus*.[12]

Charles II came to know of Talbor's success in treating the agues and appointed him King's Physician in Ordinary in 1672 much to the annoyance of the medical establishment! He was subsequently knighted in 1678. With his royal endorsement, he decided to move to London in 1672 where he established himself as a fevrologist (literally, a specialist in fevers). There he published his famous book on fevers, *Pyretologia,* the preface of which began with the following verse:

> The learned author in a generous Fit; T'oblige his Country hath of Agues writ; Physicians now shall be reproacht no more; Nor Essex shake with Agues as before; Since certain health salutes her sickly shoar.

What indeed was Talbor's secret and the basis of the English remedy? In fact it seems to have been relatively simple: he gave larger doses of the Peruvian bark and at more frequent intervals, and did not bleed or purge his patients. Moreover, he administered the bark immediately after a shivering fit and then used smaller doses to prevent relapse. His only gesture to the then-prevalent polypharmacy was to infuse the bark in white wine and to add sweet herbs in an attempt to disguise the extremely bitter taste of the Peruvian medicine.

In 1679, Charles II asked Talbor to go to France to attempt to cure the Dauphin of a recurring ague. This endeavour proved successful and Louis XIV, in gratitude, made him a Chevalier of France and bought the secret of the English remedy from him for 2,000 Louis d'or, a considerable

sum of money in those days. Talbor stipulated that the remedy should remain secret until his death.

Talbor died in 1681. In 1682 the King of France published *Le remede Anglais pour la guerison des fievres*. Shortly afterwards an English version was published with the subtitle 'Talbor's wonderful secret for curing of agues and fevers.'[13] These two books had a dramatic effect on public opinion. The price of the bark rose across Europe, in France, for example, quadrupling from 25 francs per pound to 100 francs per pound. Matters should now have been straightforward in relation to the development of knowledge of the bark but they were not.

**BARKING UP THE WRONG TREE**

In many ways the late seventeenth century was still a pre-scientific age. No systematic botany existed to speak of (before Linnaeus), and chemistry was still dominated by the alchemists.

With the marked rise in the price of bark across Europe, cheating became rampant. Other bitter substances were used as substitutes such as cherry bark or aloes steeped in water. Bark was also sold that had been extracted once and had thereby lost 90% of its therapeutic activity. To make matters worse, by inspection of the bark it was not possible to tell how much of the active principle resided in it. No assay, biological or chemical, was available at this time. All sorts of bark were in circulation, some genuine, some not.

A particular cause for confusion was the Peruvian balsam tree which was known in South America as 'quina-quina' and had been imported for some years.[14] The bark (and balsam) of this tree was also widely distributed in Europe but its effect on fevers and agues was non-specific. Later, when scientific classification had developed, it was recognised to be a completely different genus *Myroxylon peruiferum* (Figure 3).

Other problems developed with the clinical use of the bark: fever was regarded as a specific disease, not as a symptom of many different diseases. This confusion began to be clarified by Francesco Torti, the famous Italian physician who realised that there were many different kinds of fevers and that some responded to 'China-China' (the Peruvian bark) and that some did not. In his book[15] *Therapeutice Specialis*, which became a classic, he produced an illustration of a Tree of Fevers (Figure 4). Branches of the tree covered with bark represent fevers cureable by Peruvian bark whereas denuded, leafless branches represent fevers resistant to the medication. This work by Torti was to pave the way both for the idea of a 'therapeutic trial' of a medicinal compound and for the search, in the nineteenth century, for specific animalcule pathogens.

**FIGURE 3**
**The Peruvian balsam (*Myroxylon peruiferum*).**

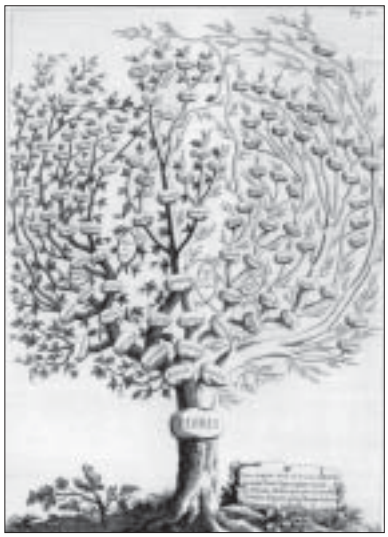

**FIGURE 4**
**Torti's Tree of Fevers. From *Therapeutice Specialis.* Modena; 1712.**

**THE SEARCH FOR THE TRUE TREE OF ORIGIN OF THE PERUVIAN BARK**

With the increased demand for the bark, its rising price, and the confusion over the identity of the tree from which the bark was derived, it now became essential to locate the tree in its native habitat. It was also hoped to identify more widely distributed forests in order to increase commercial production.

In 1735, the French Government sent an expedition to South America.[16] Ostensibly the prime aim of the expedition was to measure an arc of the meridian at Quito in Ecuador to determine the shape of the earth. The expedition was led by Condamine (Figure 5) and included Godin, Bouguer and Jussieu. Apart from the astronomical observations, a secondary, less well publicised, objective of the expedition was to find the fever tree. Condamine succeeded in doing this in the Sierra de Cajamina about 20 miles from Loxa (or Loja) in Peru.

On his return to Paris in 1738, Condamine published

**FIGURE 5**
**Charles Marie de la Condamine (1701–1774).**

his monograph *Sur l'arbre du Quinquina* which contained the first clear and detailed illustration of the fever (or quinquina) tree (Figure 6).[16] On the basis of this illustration and further specimens, sent to him by Condamine, Linnaeus in 1742 included this plant in his *Genera plantarum* under the title Cinchona. It should have been called Chinchona but Linnaeus's mistake has never been corrected in spite of prolonged discussion at several international conferences!

**FIGURE 6**
**The Cinchona tree from Condamine's *Sur L'arbre du Quinquina* (1738).**

Following the French expedition the trade in the bark once again developed rapidly, and Loxa at 3°59' south and 79°16' west became its centre. The route from the Loxa region to Europe was a long and difficult one: the town lies about 200 miles from the sea at Paita. From there it would be shipped up the west coast of South America to the isthmus of Panama and across, at this narrow point, to the Caribbean. Then it would be transhipped usually to Havana in Cuba, and then onwards to Seville in Spain via Cadiz.

In the latter part of the eighteenth century matters became chaotic again. In the early days, the Jesuits had taught the cascarilleros, the bark cutters, to plant five cuttings in the form of a cross for every Cinchona that was felled; this injunction was sadly forgotten as trees were torn down without replacement. The bark was often adulterated with that of other trees. Moreover, widespread smuggling took place to try and outwit the Spanish authorities. In an attempt to control all of these factors, the Spanish Government set up a monopoly at Quito in 1790 in an attempt to improve the quality, yield and processing methods for the bark. This was particularly successful in controlling supplies, helped by the discovery of further forests, outwith Peru, in Columbia, Bolivia and Ecuador. Nevertheless, supply of the bark could barely match demand. Moreover, the Spanish colonies in South America were to enter a great period of instability, war and revolution culminating in independence under Simon Bolivar. The supply of Cinchona to Europe was threatened!

## THE GENUS CINCHONA

Before considering the next stage of Cinchona's history its modern botanical classification will be considered. Following the work of Weddell in the nineteenth century, it came to be appreciated that the genus Cinchona is a complex one. A member of the Rubiacae family, the genus comprises about 40 species.[17] In their natural habitat the trees grow to 15 to 20 metres in height. The leaves are opposite and decussate with reddish pinnate veins and a petiole. The flowers are regular, white or pink, pentamerous and grouped in racemes of apical cymes. The trees are indigenous to the eastern slopes of the Andes from Columbia in the north through Ecuador to Peru in the south. They grow at altitudes between 1,500 and 3,000 metres, from 10° north of the Equator to 20° south, in areas with substantial rainfall and relatively constant temperature. Several species have been exploited and they include: *pubescens* (Vahl.), *ledgeriana* (Figure 7), *officinalis* and *calisaya*. Many hybrids and cultivars are known.

## THE ISOLATION OF QUININE

In the late eighteenth and early nineteenth centuries a number of chemists and pharmacists attempted to discover the active principle of the bark. Some success was achieved by the Portuguese naval surgeon Bernardino Antonio Gomez who extracted an active substance from the bark which he called 'cinchonino' but he was unable to purify it further.

The problem was solved in Paris in 1820 by Pierre Pelletier and Joseph Caventou.[18] Building on Gomez's initial extraction they successfully isolated two active alkaloids, quinine and cinchonine. The structure of quinine is shown in Figure 8.

Following this important breakthrough, several physicians

**FIGURE 7**
***Cinchona ledgeriana.***

demonstrated that quinine was very effective in treating tertian and quartan fevers. Moreover, the resinous and woody residues remaining after extraction of the bark were essentially inactive. As early as 1821, Pelletier and others began to manufacture quinine and, as the sulphate, it rapidly became known and used worldwide. Pelletier and Caventou did not patent their process but in a humanitarian gesture allowed it to be produced everywhere without licensing fees, and this helped greatly in its widespread use throughout the world.

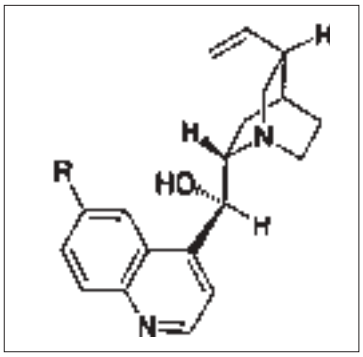


**FIGURE 8**
**The chemical structures of quinine.**

From 1820 onwards, for more than 100 years, determined attempts were made to synthesise quinine. The problem resisted all these efforts until 1944, when at Harvard, Robert Woodward and William Doering succeeded. However, the process was lengthy, complicated and expensive. As a result it did not become a commercial threat to the extraction of the alkaloid from the bark of natural Cinchona. The struggle to synthesise quinine from smaller molecules did generate one unexpected and dramatic bonus. In 1847, at the age of 18, W.H. Perkin, whilst attempting to produce quinine, instead produced the first aniline dye, mauveine, by accident.[19] This, indirectly, led on to two great developments: the aniline dye industry and, via methylene blue, to the first synthetic antimalarial compound pamaquine. This compound was first used clinically in Hamburg in 1925 where it successfully cured malaria.

Apart from the isolation of the pure alkaloids, another great benefit came immediately from the work of Pelletier and Caventou. It allowed samples of bark to be assayed for their content of quinine (and other alkaloids) initially by gravimetric and later by fluorescent methods. Cinchonas could be compared for alkaloid content and the effect of light, humidity and temperature ascertained in the production of the active compounds by the plant, factors which were to prove of supreme importance in the struggle for Cinchona.

**THE SCRAMBLE TO CULTIVATE CINCHONA OUTSIDE SOUTH AMERICA: IMPERIAL ECHOES**

The French, British and Dutch Governments all had colonies in either South East Asia, India, or Africa. These areas were plagued with recurrent fevers (or malarias as they came to be known) which were hindering economic development and threatening their military domination. If Cinchona trees (or their seeds) could be taken from South America (with or without permission) and established in a suitable location elsewhere, this would help exploitation of these colonies. Moreover, it would establish the tree outside the volatile political situation in the new South American republics.

Many attempts were made and a brief outline will be given here. The first effort was that of Condamine in 1743 when, returning from his South American expedition, his ship met a severe storm in the Amazon and his prized Cinchona trees were swept overboard! The French then tried to grow Cinchona in Algeria but failed as the area chosen was too dry. The first partial success was achieved by the French botanist, Weddell.[20] A noted authority on the classification of Cinchonas, he returned to his homeland in 1849 carrying seeds of *Cinchona calisaya*. These were successfully germinated in Paris, London and Holland. Eventually, the Dutch sent a young tree derived from this seed to Java where it flourished. It is believed to be the first Cinchona tree to have been cultivated outside South America.

France largely failed in its efforts to establish viable plantations but Britain succeeded, at least for a time, mostly due to the efforts of Clements Markham.[21] In 1859 Markham, a clerk in the government in London, was commissioned to collect young trees and seeds from the eastern Andes and acclimatise them to India and Ceylon. He went to the most promising areas accompanied by Pritchett, Cross and Spruce. The first batch of plants was sent from Peru in May 1860 and reached India in September; by December all had died! However, in April 1861 Robert Cross arrived with a second batch of plants

which were raised initially in the Botanic Garden at Ootacamund. Later they were transferred to the Nilghiris Hills in south India, near Madras, where at 7,000 feet they found conditions similar to those of the eastern Andes.[21]

By 1866 these plantations, established in India and also in Ceylon, were able to supply London with adequate amounts of bark (and hence quinine). Unfortunately this happy situation was not to continue indefinitely. Many of the trees succumbed to attack by insects, and the yield of quinine from the bark of the varieties established in India could not compete with *Cinchona ledgeriana* which had been introduced successfully into Java. Eventually the Indian growers would switch production from Cinchona to tea!

The forgotten men of this saga are Charles Ledger (Figure 9) and his Amerindian servant Manuel Incra Mamani (Figure 10). For almost 20 years the two explorers collected bark and seeds on the Peruvian/Bolivian border in the period from 1844 to 1865.[22] Eventually Ledger hit on a fine quality bark that was found to contain as much as ten per cent of the alkaloids by weight and subsequently the species came to be named *C. ledgeriana* in his honour (Figure 7). Manuel Incra Mamani obtained seeds of this species for Ledger in 1865, who sent them on to his brother, George, in London. The British Government showed little interest but the Dutch authorities bought one pound of the seed for 100 guilders (about £20) and when planted in Java they formed the basis of the world's present supply! By careful cultivation and experimentation in Java the yield from the bark of *C. ledgeriana* was doubled when compared with the wild variety in Peru and Bolivia.

**FIGURE 9**
**Charles Ledger (1818–1905).**
(Reproduced with permission from *The Life of Charles Ledger (1818–1905). Alpacas and Quinine. A digression on the exploitation of Ledger's seeds* by G. Gramiccia. Macmillan Press: Basingstoke and London; 1988.)

**FIGURE 10**
**Manuel Incra Mamani. He died for Cinchona seeds.**
(Reproduced with permission from the Museum of the Royal Pharmaceutical Society of Great Britiain.)

The story ends in tragedy. In 1871 Manuel went on another seed collecting trip but was arrested by the police. He refused to reveal for whom he was collecting and was imprisoned for 20 days and beaten badly. Shortly after his release he died at his own home. Ledger was grief-stricken by this loss and stopped all seed collecting immediately. He also cared for Manuel's family with money and other help.[23]

Ledger retired to New South Wales but lost all his money in the Australian banking crash of 1891. Belatedly, in 1896, the States General of Holland voted him a pension of £100 per year for 'distinguished services rendered to the Cinchona industry'. Ledger died in 1905, his death passing largely unnoticed. A recent biography by Gramiccia has been a fitting tribute to his life and work.[22]

The Javanese plantations of Cinchona flourished under the careful stewardship of the Dutch horticulturalists and by the 1920s produced most of the world's quinine. In 1942 the Japanese captured Java and the Cinchona fields were no longer available to the Allies. This led to a worldwide shortage of quinine and also to an immediate emphasis on the production of synthetic antimalarials such as mepacrine and chloroquine. The search for natural plant products active against malaria was effectively abandoned.

## THE MALARIAL PARASITE REVEALED

By the middle of the nineteenth century it was clear that quinine acted as a 'specific' remedy in malarial fever but, as Torti had suggested, was inactive in others. Then physicians started to suggest that quinine might act by killing a parasitic or invasive living organism: a fungus

was suggested as a candidate by Mitchell in 1849 or alternatively a bacterium by Klebs and Tommasi-Crudeli in 1879.

In 1880 came a breakthrough. Alphonse Laveran was a surgeon working in the military hospital at Constantine in Algeria (Figure 11); he started to look under the microscope at fresh blood smears from patients with 'malaria'. At the periphery of the smears he noticed some mobile elements. He thought that they resembled protozoa and also observed that from time to time they emitted extremely motile flagellae. He called his new found organism *Oscillaria malariae* in view of the very active flagellae and the association with malaria.[24] Modern interpretation of his observations would call the 'animalcules' the gametocytes of *Plasmodium falciparum*.

**FIGURE 11**
**Charles Louis Alphonse Laveran (1845–1922).**

Much further work by many investigators including Marchiafava, Golgi, Celli, Grassi, Manson and Ross would establish the different forms of *Plasmodium* (as the parasite came to be called) and the life cycle involving the critical phase in the Anopheles mosquito. For an excellent account of this phase of the fight against malaria the reader is referred to the book by Poser and Bruyn.[25]

## THE ACTIONS OF QUININE

When the parasite had been identified (together with its asexual and sexual forms) its life cycle and the action of quinine upon the phases could be established. Basically, quinine appears to be a schizonticide acting on the intraerythrocytic asexual forms. It has no action against the sporozoites (or the tissue stages) and is virtually inactive against the gametocytes. The mechanism of action seems to be rapid uptake into the red blood cells followed by inhibition of protein synthesis in the parasite.[26]

Quinine still has a place in the modern treatment of malaria where it is used in severe and complicated falciparum malaria; and in this type of malaria where drug resistance to the 4-aminoquinolines or the combination of sulphadoxine/pyrimethamine has developed. Minor uses of the alkaloid include the prevention of nocturnal muscle cramps and the alleviation of myotonic contractions in Thomsen's disease (myotonia congenita).[26] Quinine is also used as a bitter agent in drinks (and other flavourings), and as a source of quinidine (the cardioactive drug).

## CONCLUSION

It is now almost 400 years since the Jesuits in Peru identified the bark of the Cinchona, brought to them by the Amerindians, as having a specific febrifugal effect. At first there was the bark but no tree, and then the tree but no compound, then the substance quinine but no chemical structure or effective synthesis. Finally the parasite *Plasmodium* was identified and the facts were fitted together to form a coherent picture.

It is a saga involving many elements: bravery, generosity, greed, exploitation and the colonial ambitions of the great European powers. Heroes and villains abound throughout. As we sip our gin and tonic (containing, of course, quinine) we should reflect on the bark collectors; the Jesuits and de Lugo; Condamine, Pelletier and Caventou; Mamani and Ledger; and Laveran (and many others). We should give thanks and raise a glass to all who served in the quest for quinine!

## ACKNOWLEDGENTS

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## REFERENCES

1 Jaramillo-Arango J. A critical review of the basic facts in the history of Cinchona. *J Linnaean Soc* 1949; **53:**1272–309.
2 Paredes-Borja V. Contribucion del Ecuador a la Materia Quimica: la Quina. Ecuador; 1946. (Three year II (January–December) pp. 217 et sequitur.)
3 *Op. cit. ref.*1, 283–4.
4 Jarcho S. *Quinine's Predecessor. Francesco Torti and the early history of Cinchona.* Baltimore and London: John Hopkins University Press: 1993; 16–17.
5 Poser CM, Bruyn GW. *An Illustrated History of Malaria.* New York and London: Parthenon Press; 1999; 79–80.
6 *Op. cit. ref.*1, 285.
7 Redi F. *Opere de Francesco Redi.* Venice: Ertz; 1712–50.
8 McMains HF. *The Death of Oliver Cromwell. 'Malaria.'* Kentucky: University of Kentucky Press; 2000; 86–8.
9 Bruce-Chwatt LJ. Oliver Cromwell's Medical History. *Transact Coll Phys Philadelphia* 1984; **4:**98–121.

10 *Op. cit. ref.* 8 'Poisons metallic and vegetable.' 94–5.
11 Dobson MJ. Bitter sweet solutions for malaria: exploring natural remedies from the past. *Parassitologia* 1998; **40:**69–81.
12 *Op. cit. ref* 11. footnote to page 69; History of malaria in England. *J Roy Soc Med* 1989; **82:**3–7.
13 Talbor R. *The English Remedy: or Talbor's wonderful Secret for cureing Agues and Fevers*. Sold by the author Sir Robert Talbor, to the most Christian King, and since his death, ordered by his Majesty to be published in French, for the benefit of his subjects, and now translated into English for public good. London: Printed by J. Wallis for J. Hindmarsh; 1682.
14 *Op. cit. ref.* 5, 79–80.
15 Torti F. *Therapeutice Specialis ad Febres Quaedam Perniciosas*. Modena: B. Soliani;1712.
16 de la Condamine C. Sur l'arbre du Quinquina. *Acad Roy Sc Paris;* 1738.
17 Bruneton J. *Pharmacognosy; Phytochemistry and Medicinal plants*. 'Cinchona.' Paris: Lavoisier Publishing: 1995; 846–52.
18 Pelletier P, Caventou J. Recherches chimiques sur les quinquinas. *Ann Chim Phys* 1820; **15:**337–67.
19 Garfield S. *Mauve: How one man invented a colour that changed the world.* 'Quinine'. London: Faber and Faber; 2000; 30–4.
20 Weddell H. *Histoire naturelle des quinquinas*. Paris: Victor Masson; 1849.
21 Markham, C. *Peruvian Bark*. London: John Murray; 1880.
22 Gramiccia, G. *The Life of Charles Ledger (1818–1905). Alpacas and Quinine*. 'A digression on the exploitation of Ledger's seeds.' Basingstoke and London: Macmillan Press; 1988; 153–65.
23 *Op. cit. ref.* 22, 135–7.
24 Laveran A. Note sur un nouveau parasite trouve dans le sang de plusieurs malades atteints de fievre palustre. *Bull Acad Med Paris* 1880; **9:**1235–6,1346–7.
25 *Op. cit. ref.* 5.
26 Dollery CT (ed.) *Therapeutic Drugs*. Volume 2. Quinine Q8–Q13. Edinburgh: Churchill Livingstone; 1991.