Cinchona: endangered tree from South America, antidote for malaria and presidential pharma

Both chloroquine and hydroxychloroquine have featured regularly in world news in the weeks of the Covid-19 pandemic but what is *hydroxychloroquine*? Perhaps we should start with *chloroquine*, an anti-malarial medication used to treat malaria. Malaria is caused by a *Plasmodium* parasite transmitted by the bite of *Anopheles* mosquitoes. It affects ~ 40% of the world's population and is responsible for more than a million deaths each year.

Chloroquine is a member of the drug class 4-aminoquinoline and works against the asexual form of the malaria parasite within the red blood cells. It works fast, has a low level of toxicity, and is well tolerated. However, the widespread use of chloroquine led to the emergence of resistance, starting in South-East Asia and now spreading to almost every malaria prone region of the world. *Hydroxychloroquine* was developed to manage malaria in areas where strains of malaria were resistant to *chloroquine.*

US president Donald Trump has touted the benefits of the anti-malarial drug *hydroxychloroquine* as a protection against Covid-19 but unsurprisingly, it makes for a confusing tale. Federal regulators warned of the potential dangers of the drug but WHO trials have since recommenced a retraction of a paper in *The Lancet.*

Prior to *Hydroxychloroquine* and *Chloroquine* was *Quinine*, an alkaloid, a naturally sourced derivative from the bark of *Cinchona* trees of South America. Malaria was *not present* in the Americas prior to the arrival of Europeans in 1492, however, the Quechua people of Peru, Bolivia and Ecuador used the ground bark in sweetened water as a muscle relaxant and to halt shivering due to low temperatures. The Spanish learnt about *Cinchona* from the indigenous Quechua, possibly as early as the 1570s, and Jesuit missionaries brought it back to Europe to use in combating malaria, endemic in swamps and marshes surrounding Rome (hence its name, 'bad air'). The first use of *Cinchona* in Europe was in 1631.

Cinchona officinalis, Rubiaceae, Quinine Bark, bark. H. Zell / CC BY-SA (https://creativecommons.org/licenses/by-

Malaria posed an on-going problem for colonisation of Africa by European nations; quinine provided a means of overcoming this obstacle and tonic water (diluted generally with gin) gained a reputation as a way of warding off malaria. Quinine was first isolated from *Cinchona* bark in 1817.

In the early 1800s, Peru, together with other South American countries, outlawed the export of *Cinchona* seeds and plants in order to maintain their monopoly on the tree bark. To counteract this, the Dutch smuggled seeds out of South America and set up *Cinchona* plantations in Indonesia, and by the 1930s, were producing 97% of the world's quinine production.

So what of the origins of Cinchona? There are about 23 species of *Cinchona*, a genus in the Rubiaceae family which includes coffee, *Gardenia*, *Hydrangea*, *Luculia* and *Coprosma*. All

Cinchona species are evergreen, and all are natives of South America where they grow in mountainous regions of Venezuela, Columbia, Ecuador, Peru and Bolivia.

In Peru, home to 20 species, sadly, *Cinchona* is at risk from deforestation, soil degradation and the replacement of forests with agriculture.

Cinchona calisaya by Franz Eugen Köhler - https://commons.wikimedia.org/w/index.php?curid=5235191

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Flückiger F A, Hanbury D. 1874. *Pharmacographia: A History of the Principal Drugs of Vegetable Origin, Met with in Great Britain and British India*. MacMillan and Co., London.

[1]Tom McCarthy & Joan E Greve, *The Guardian*, Wed 20 May, 2020 0905 AEST.

Cortijo, R. 2018. *Peru in danger of losing its national Cinchona* tree. Phys.Org: https://phys.org/news/2018-10-peru-danger-national-*Cinchona*-tree.html

Sáenz F E, Mutka T, Udenze K, Oduola A M J, Kylea D E. 2012. Novel 4-Aminoquinoline Analogs highly active against the blood and sexual stages of *Plasmodium In Vivo* and *In Vitro*. *Antimicrobial Agents and Chemotherapy.* 56(9): 4685 – 4692.

Wikipedia: https://en.wikipedia.org/wiki/Artemisinin#Artemisinin_derivatives

Wikipedia: https://en.wikipedia.org/wiki/Quinine_total_synthesis

Wikipedia: https://en.wikipedia.org/wiki/Cinchona

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