International Journal of Medical Science and Clinical Invention 7(5): 4795-4801, 2020
DOI:10.18535/ijmsci/v7i05.02 **ICV: 77.2**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Research Article,

Cinchona Bark for the Treatment of Covid-19 Pneumonia: A Modern Review of the Potential Anti-Viral Therapuetic Applications of an Old Treatment

Inklebarger J[1], Gyer G[2], Galanis N[3], Adel Ghulam[4], Michael J[5]

[1,4]The London College of Osteopathic Medicine, 8-10 Boston Place, London NW1 6QH, UK
[2,5]Wimpole St, Marylebone, London WTU 1PH
[3]Aristotle University of Thessaloniki

Abstract:

Purpose: The Coronavirus 2019 (COVID-19) pandemic is an international public health emergency. Vaccines and acute infection drugs are currently unknown, and when available, expense and distribution issues may impede distribution in underserved areas. The aim of this systematic review was to summarize the evidence regarding cinchona bark (CB) for its potential anti-viral properties against COVID-19
Study design: A current literature and historical text review was conducted, limited to articles having full text or abstracts available in English, using Google Scholar, PubMed-NCBI, Science Direct, and WebMD, and online book publications, with key search words, including synthetic CB analogues: chloroquine-hydroxychloroquine (CQ/HCQ) derivatives.
Results: Several related in-vitro studies, editorials, and expert consensus papers on quinine analogue anti-viral treatment papers and historical treatises have been published. A March 2020 CQ drug train ongoing in China, recently reported breakthrough efficacy evidence for COVID-19 pneumonia. However, there are currently severe CQ shortages, and direct evidence for CB use is sparse, several centuries old, and controversial.
Conclusion: CB was for centuries known to be a natural source of quinine from which modern synthetically manufactured analogues anti-viral purposed drugs such as CQ/HCQ are based. CB may also possess anti COVID-19 activity as its historical derivatives, but with the same potential for life-threatening adverse reactions and severe drug interaction complications akin to its analogues. Issues with herbal quality control, prescriber dose inexperience, perceived risk underestimation by self-prescribers, and a misinformed propensity for consumer fraud is other concerns. However, analogue drug risk-benefit ratios indicate CB may also have some value for acute COVID-19 (cytokine storm) infection management. Existing and evolving CQ evidence efficacy, shadowed by shortages, may highlight a need for modern and timely investigation of CB as a cost-effective alternative COVID-19 pneumonia therapy.

Keywords: Cinchona, Bark, Quinine, COVID-19, SARS-CoV, RNA-Virus, Herbal, Fever Tree, Chloroquine, Hydroxychloroquine

Introduction:

The December 2019 rapid worldwide spread of severe acute respiratory syndrome coronavirus 2 (COVID-19) originated in Wuhan China, with 24 March 2020 reports derived from 195 countries, listing 81,767 cases, with 3281 deaths. It was WHO (World Health Organization recognized as a pandemic on 11 March 2020. [WHO.Novelcoronavirus (COVID-19) situation, 2020], and as of 21 March 2020, viral pathogenesis and proliferation pathways remain unknown, challenging treatment. [Zhou P et al 2020, Howard et al 2012] As of yet, no drugs or vaccines for COVID-19 are specifically known, [Wu Z et al 2020], though novel antiviral drugs (Remdesiver, Favipiravir) are being investigated.

[Lu H 2019] Prescription drug unavailability, expense, patient preferences, alternative and folk medicine traditions, has driven a demand for plant-based therapeutic alternatives. Since prehistoric times, botanical preparations have been used to treat a variety of diseases and the remain an important part of current pharmacopeia. The World Health Organization (WHO) also estimates that 80% of the population of developing countries continue to rely of traditional plant-based medicines. [Bennerman et al 1983, Mahady 2001], unfortunately, with the advent of mass produced pharmaceuticals, (many of which were originally plant-based), much of mankind's arcane historical ethno botanical knowledge and oral traditions have been forgotten, with their current cultural importance overlooked. Surviving records and systems such as the Susruta Samhita and Traditional Chinese Medicine have also been collectively editorialized and dismissed as pseudoscience. Nevertheless, 25% of common prescription drugs still contain isolated plant constituents. [Rees et al 1993] and may supplement the sub-optimal global availability of essential medicines. [Parker-Lue S et al 2015] Cinchona bark, a historical natural source of quinine, was once the source of anti-viral chloroquine analogues currently being tested against SARS-cov 19. However, with the advent of modern industrial scale drug synthesis, the therapeutic uses of quinine bark itself have largely been relegated to history. This paper revisits the potential use of CB as an acute anti COVID-19 monotherapy.

Materials & methods:

A material search was limited to articles having full text or abstracts available in English. Google Scholar, sciencedirect, and WebMD publications were reviewed utilizing primary search words of COVID-19, SARS, cinchona, cinchona, fever tree, antiviral, herbs, herbal medicine, herbal formulations, medicinal plants, traditional medicine, folk medicine etc. Searches were also conducted using the historical names of the cinchona/chinchona plant, and its analogue drugs for toxicology profiles, mechanisms of action, and anti-malarial, Rheumatology, Neurology (restless legs syndrome), Cardiology (anti-arrhythmic), and potential antiviral applications. Bibliographical and historical references and the conclusions of source primary studies were also searched for additional relevant references.

The medicinal history of cinchona:

Quinine derived from the 'fever tree' has a long, prominent, and controversial history as a remedy against malaria. CB remains inexpensive and is easily obtainable without prescription (eBay). Synthetic derivatives have also had existing familiarity as a Rheumatology anti-inflammatory drug, and it is a tonic water ingredient and its analogues have also been known to have anti-viral properties. The medicinal properties of cinchona fever trees were known to pre-European contact South American cultures. Some contend that CB was not utilized in Europe until the 19th century. Though disputed, it was not until 1663 that the first cinchona bark (CB) malaria treatment allegedly involving the 4th Countess of Cinchon of Lima Peru was recorded. [Meyer CG et al 2004] Jesuit missionaries also contributed material and medicinal knowledge transfer of CB back to Europe. [Crawford MJ et al 2014, Sequeira JH 1929] The trial and error recipes of the 1649 '*Schedula Romana*' may have been based on even more ancient Roman works. [Jarcho S 1993] With a Chicora bark side effects treatise published by Magendie several years later. [Magendie F 1822] Another 'picturesque story' of the medicinal discovery of CB was described in a 1928 issue of the British Medical Journal. He narrated the legend of a fever-stricken South American Indian how fell asleep after drinking water from a lake in which a cinchona tree had fallen, awakening with his fever cured. [Thompson CJS 1928] Considered a disease of the tropics, malaria killed many 17th century European peasants, Kings, and Popes with outbreaks during the Gulf of Finland swamp drainages and construction of Saint Petersburg Russia. CB was originally native to the Andean region and forests of South America. Species of these rapidly growing trees and shrubs are found abundantly throughout the tropical world, and are now even regarded as nuisance plants, with there anti-malarial properties largely forgotten. [Bennermen et al 1983, Mahady 2001] CB recipes and therapeutic dose information for the bark powder appears to have now been virtually lost to modern science too, though its beneficial derivatives of chloroquine and hydroxychlorquine have been known since 1934. Later

immunomodulatory auto-immune applications of these drugs have popularized their role in managing rheumatoid arthritis, systemic lupus, juvenile rheumatoid arthritis. [Jorge A et al 2018] Both Chloroquine (CQ) and Hydroxychloroquine (HCQ) have proven efficacy in suppressing the trajectory progression of these diseases with limited and reversible toxicity, particularly with their short-term use. [Melles RB et al 2014]. CQ/HCQ tolerability, low cost, and immunomodulatory properties also suggest a potential use in viral infections and their inflammatory response. [Savarino A et al 2001, Boelaert JR et al 2001]. The anti-inflammatory properties of CB-derived chloroquine, is also believed to temper immune hyper activation reactions, which characterize HIV/AIDS. [Savarino A et al 2000] This property might prove useful in controlling the cytokine storm that occurs late-phase in critically ill SARS-cov-2 infected patients. [Yao X et al 2020] Quinine and CQ/HCQ have also been prescribed for restless legs syndrome, as these are believed to reduce the excitability of motor endplates and prolong the leg muscle latency period. [Brunton L.L. et al 2011]

The safety profile of chicona bark:

Though some researchers consider quinine, CQ/HCQ to be essentially safe, therapeutic and above therapeutic doses may have serious or deadly consequences. Intentional or inadvertent overdose have been linked to serious and even fatal cardiac arrhythmias, with fatal poisoning being of particular concern in young children. [Achan J et al 2010. Bar-Oz B et al 2004]. Interactions with anti-clotting medications [Mandel E.H. 1962] and anti-epileptics have also been reported.

The side effect cluster of CB or quinine ingestion is known as 'Cinchonism.' Mild symptoms include diarrhea Flushing, sweating, tinnitus, blurred vision, reversible high-frequency hearing deficit, confusion, headache, abdominal pain, photo-sensitivity is known. Larger quinine doses may lead to more severe but reversible symptoms, such as dizziness, transient blindness, cardiomyopathy somnolence, suicidal ideation, and anaphylactic shock (Backwater fever). However in non-severe cases most symptoms abate upon cessation. [Vinetz JM 2017] Severe drug interactions have also been reported with aluminum-containing antacids, cholinesterase inhibitors, cimetidine, digoxin, neuromuscular blocking agents, warfarin and other agents can take place. [Bruton LL et al 2011] Despite these side effects, synthetic CQ and HCQ analogues, have over 50 years of prescription experience, demonstrating reassuring acute administration safety profiles in the management of Rheumatological diseases. Adverse CQ/HCQ adverse events usually present only after several years of prescribing, with the most serious toxic effects being macular retinopathy. Toxicity is also cumulative rather than daily-dose dependent, and permanent retinal damage may be prevented by vision monitoring during treatment. [Bernstein HN 1991, Bernstein HN 1993, Herman K et al 2002] Other publication provided further reassuring ocular safety profile evidence with even 500 mg per day of high-dose CQ for the management of Rheumatology conditions during pregnancy. [Klinger G et al 2001] Savarino and colleagues further concluded that CQ/HCQ administration presents with limited and well-preventable toxicity profile, and low risk/benefit balance especially in life-threatening conditions such as SARS (a COVID-19 like RNA virus) and AIDS. [Savarino A et al 2003]

Results:

Cinchona bark May as its analogues, have reported therapeutic activity against Plasmodium Malaria, human immunodeficiency viruses, (AIDS), picornavirus (rhinovirus or enter virus, orthomyxo influenza viruses, paramyxoviruses (parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV), a coronavirus, e.g., SARS viruses such as COVID-19. Naturally occurring CB and its man-made compositions of CQ/HCQT therapeutically or prophylactically treats protozoal and viral infections, targeting diseases RNA viruses and retroviruses. Species potency, and recommended doses are historically arcane and side effects range from mild and reversible to irreversible and life threatening.

Discussion:

CB has a long and colourful history as an anti-malarial treatment. However, it wasn't until the mid-20th century that the first Quinine antiviral animal model study was published. [Seeler A.O. et al 1946] Dengue (DENV-2) like COVID-19 is an RNA virus and a 2018 control group Quinine

efficacy study also noted a rather dramatic dose-dependent 80% DENV-2 virion protein reduction. [Malakar S et al 2018]

Figure 1: Chicora powder, tree and bark

Due to low toxicity, low cost, high tolerability, immunomodulatory, and anti-inflammatory properties, two drugs originally derived from CB (CQ and HCQ) have been proposed for use against viral infections. Though specific anti-viral mechanisms are currently unclear, anti-viral and strong anti-inflammatory activity are well known. Proposed anti-viral mechanisms of actions of CB these derivatives include the inhibition of cytokine production (management of cytokine storm), and T cells release of IL-1, 2, 6, or 18, tumor necrosis factor TNF-α and IFN-γ, reduced levels of chemokines CCL2 and CXCL10, inhibition of micro-RNA expression, decreased TH17-related cytokines, decreased DNA, RNA and protein synthesis in thymocytes. [Al-Bari M.A 2015]. They may also represent an anti-inflammatory alternative to corticosteroids, which have an inherent risk of pulmonary super infection in the critically ill, and as a co-treatment may lessen the dose of more expensive anti-retrovirals. [Savarino A et al 2003] Specifics of CB dosages have been largely forgotten, probably due to the widespread use of synthetic chloroquines. Some specifics of treatment may be found in the 1649 'Schedula Romana' pharmaceutical handbill, which reported that it was better to the powdered CB bark in wine rather than water, presumably due to the former affording greater alkaloid solubility. This another arcane texts, have afforded a full three centuries of reasonable quinine dosage calculation. [White NJ 2013] Savarino and colleagues evidence-based reviews also concluded a desirable risk to benefit ratio, citing of CB derived CQ/HCQ, with high efficacy, and limited preventable toxicity, rendering them a viable option against the sometimes lethal and quick immune-host reactions of those infected with RNA viruses such as COVID-19. [Savarino A et al 2003] As CB is the parent substance from which CQ/HCQ was originally derived, the bark itself may be a viable acute anti-COVID-19 management too. The bark's availability, minimal processing requirements, low cost, ease in transport, potential efficacy, and apparently acceptable risk to benefit safety profile, potential coverage mutated forms, may make also it a feasible option for managing the critically ill in underserved populations who might otherwise have not treatment at all. Further CB innovations, such spray forms may prove to have protective barrier properties it may find use as a less harsh and costly alternative to anti-viral cleaning solutions. CB species-related potency differences, product contamination, impurities, improper handling, and consumer fraud, and it is historical monopolization and destruction of cinchona tree-forest habitat would not be repeated. [Jaramillo-Arango J 1949] Due to CB being an abundant natural resource requiring little processing, acquiring funding for RCT trials may be difficult.

Conclusions:

CB has antiviral and immunomodulatory effects that warrant further study, for it may have a role in both the prevention and treatment of COVID-19 infection. Potential serious analogue drug side effects may also be akin to CB, warranting like caution. However, the literature suggests that CB like CQ may afford a well-preventable toxicity profile and desirable risk-benefit balance, particularly when contemplating treatment of life-threatening conditions such as acute SARS-cov [Savarino A et al 2003, Peiris JS et al 2003]. Recent 'breakthrough CQ efficacy evidence from China looks promising. [Gao J et al 2020] However, severe CQ shortages, [Moore N 2020], indicate that further research, testing, and timely investigation of CB's efficacy may be warranted, as the bark may be more economical, available, and require less processing that its drug derivatives.

Acknowledgements: Special thanks to Dr Amir Akhtar for proofreading.

References:

[1.] Achan J., Talisuna A.O., Erhart A., Yeka A., Tibenderana J.K., Baliraine F.N., Rosenthal P.J., D'Alessandro U. Quinine, (2011) An old anti-malarial drug in a modern world: Role in the treatment of malaria. Malar. J; 10:144. Doi: 10.1186/1475-2875-10-144. [PMC free article] [PubMed] [Crossref] [Google Scholar]

[2.] Al-Bari M.A. (2015), Chloroquine analogues in drug discovery: New directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J. Antimicrob. Chemother. 70:1608–1621. Doi: 10.1093/jac/dkv018. [Pubmed] [Crossref] [Google Scholar]

[3.] Bar-Oz B., Levichek Z., Koren G. (2004), Medications that can be fatal for a toddler with one tablet or teaspoonful. Paediatr. Drugs; 6:123–126. Doi: 10.2165/00148581-200406020-00005. [PubMed] [Crossref] [Google Scholar]

[4.] Bennerman R, Burton J, Chen WC, Editors, (1983), Medicinal plants and primary health care: an agenda for action. Traditional medicine and health care coverage; Geneva, Switzerland: World Health Organization

[5.] Bernstein HN. (1983), Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. Is J Med; 75: 25–34?

[6.] Bernstein HN. (1991), Ocular safety of hydroxychloroquine. Ann Ophthalmol; 23: 292–96.

[7.] Boelaert JR, Piette J, Sperber K. (2001), the potential place of chloroquine in the treatment of HIV-1-infected patients. J Clin Vir; 20: 137–40.

[8.] Brunton LL, Chabner BA, Knollmann BC, editors. (2011), Quinine and quinidine. In: Goodman & Gillman's the pharmacological basis of therapeutics. 12th ed New York: McGraw-Hill; 1405–7. [Google Scholar]

[9.] Crawford, Matthew James (2014). "An Empire's Extract: Chemical Manipulations of Cinchona Bark in the Eighteenth-Century Spanish Atlantic World". Osiris. 29 (1): 215–29.

[10.] Howard CR, Fletcher NF. (2012), emerging virus diseases: can we ever expect the unexpected? Emerging Microbes Infect; 1:1–11. Doi: 10.1038/emi.2012.13. [PMC free article] [PubMed] [crossref] [Google Scholar]

[11.] Gao J, Tian Z, Yang X (2020), Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies, Biosci Trends16; 14(1):72-73. Doi: 10.5582/bst.2020.01047. Epub 2020 Feb 19.

[12.] Herman K, Leys A, Spileers W. (2002), Hydroxychloroquine retinal toxicity: two case reports and safety guidelines. Bull Soc Belge Ophtalmol; 284: 21–29.

[13.] Jaramillo-Arango, Jaime (1949). "A critical review of the basic facts in the history of Cinchona". Journal of the Linnean Society of London, Botany. 53(352): 272–311.

[14.] Jarcho S. (1993), Quinine's Predecessor: Francesco Torti and the Early History of Cinchona, Baltimore: Johns Hopkins University Press [Google Scholar]

[15.] King C. (2008), Exhibits tubercin activity; immune enhancers such as glycyrrhizin

(GR), glycyrrhetic acid and Chinese herbal extracts. Google Patents

[16.] Klinger G, Morad Y, Westall CA, et al. (2001), Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. Lancet; 358: 813–14.

[17.] Magendie F (1822 [1829, 2nd edn]). Formulaire pour la préparation ET l'emploi de plusieurs médicaments [Formulations for the preparation and the usage of several drugs]. Paris: Imprimerie de Plassan.

[18.] Mahady GB. (2001), Global harmonization of herbal health claims. J Nutr; 131(3):1120S–1123S. [PubMed] [Google Scholar]

[19.] Malakar S., Sreelatha L., Dechtawewat T., Noisakran S., Yenchitsomanus P.T., Chu J.J.H., Limjindaporn T. ((2018), Drug repurposing of quinine as antiviral against dengue virus infection. Virus Res. 2018; 255:171–178. Doi: 10.1016/j.virusres.2018.07.018. [PubMed] [Crossref] [Google Scholar]

[20.] Mandel EH, (1962), the anticoagulant properties of chloroquine dihydrochloride (Aralen), hydroxychloroquine sulfate (Plaquenil), and quinine dihydrochlorine. Results of tests in vitro, J Mt Sinai Hosp N Y; 29:71-3.

[21.] Melles RB, Marmor MF. (2914), the risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol; 132(12):1453-60. [PubMed]

[22.] Meyer CG, Marks F, May J, (2004) Editorial: 'Gin tonic revisited'. Tropical Medicine & International Health. 9(12):1239-40

[23.] Moore N, (2020), Chloroquine for COVID-19 infection, Drug Saf, 7:1–2. Doi: 10.1007/s40264-020-00933-4 [Epub ahead of print]

[24.] Parker-Lue S, Santoro M, Koski G. (2015), the ethics and economics of pharmaceutical pricing. Annu Rev Pharmacol Toxicol; 55:191–206. Doi: 10.1146/annurev-pharmtox-010814-124649 [PubMed] [Google Scholar]

[25.] Peiris JS, Chu CM, Cheng VC, et al. (2003), Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet; 361: 1767–72.

[26.] Rees LP, Minney SF, Plummer NT, Slater JH, Skyrme DA. (1993), a quantitative assessment of the antimicrobial activity of garlic (Allium sativum) World J Microbiol Biotechnol; 9(3):303–307. Doi: 10.1007/BF00383068. [PubMed] [Crossref] [Google Scholar]

[27.] Savarino A, Bottarel F, Malavasi F, Dianzani U. (2000), Role of CD38 in HIV-1 infection: an epiphenomenon of T-cell activation or an active player in virus/host interactions? AIDS; 14: 1079–89.

[28.] Savarino A, Gennero L, Sperber K, Boelaert JR. (2001), The anti-HIV-1 activity of chloroquine. J Clin Virol; 20: 131–35.

[29.] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R, (2003), Effects of chloroquine on viral infections: an old drug against today's diseases?, Lancet Infect Dis; 3: 722–27

[30.] Seeler A.O., Graessle O., Ott W.H. (1946), Effect of quinine on influenza virus infections in mice. J. Infect. Dis; 79:156–158. Doi: 10.1093/infdis/79.2.156. [PubMed] [crossref] [Google Scholar]

[31.] Sequeira J.H. (1929), the History of Cinchona. Br. Med. J; 1:621–22. Doi: 10.1136/bmj.1.3560.621-b. [crossref] [Google Scholar]

[32.] Thompson C.J.S. (1928), the history and lore of cinchona. Br. Med. J; 2:1188–90. [PMC free article] [PubMed] [Google Scholar]

[33.] Vinetz J.M. (2017), Chemotherapy of Malaria. In: Brunton L.L., Hilal-Dandan R., Knollmann B.C., editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. Mcgraw-Hill Education; New York, NY, USA [Google Scholar]

[34.] WHO.Novelcoronavirus (COVID-19) situation. Updated March 24, 2020. Https://experience. Arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd

[35.] White, NJ (2013). "Pharmacokinetic and Pharmacodynamic Considerations in Antimalarial Dose Optimization" Antimicrob Agents Chemother. 57: 5792–807.

[36.] Wu Z,mcgoogan JM. (2020), Characteristicsofand important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. Doi: 10.1001/ jama.2020.2648

[37.] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D (2020), In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-cov-2), Clin Infect Dis. 2020 Mar 9. Pii: ciaa237. Doi: 10.1093/cid/ciaa237. [Epub ahead of print]

[38.] Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. (2020), Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. Biorxiv. [Google Scholar]