IJPSR (2023), Volume 14, Issue 3 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 June 2022; received in revised form, 02 August 2022; accepted 20 November 2022; published 01 March 2023

CINCHONA EXHIBITS CANDIDATES AS A COMPLEMENTARY ANTIVIRAL ACTIVITY FOR SARS-COV-2: A NARRATIVE REVIEW

Manikantan Pappuswamy *, Arun Meyyazhagan and Aditi Chaudhary

Department of Life Sciences, CHRIST (Deemed to be University), Bangalore - 560029, Karnataka, India.

Keywords:

COVID-19, Herbal medicine, Cinchona, Anti-Viral agents, SARS-CoV-2

Correspondence to Author:
Dr. P. Manikantan

Associate Professor,
Department of Life Sciences,
CHRIST (Deemed to be University),
Bangalore - 560029, Karnataka, India.

E-mail: manikantan.p@christuniversity.in

ABSTRACT: Aim and Objective: The coronavirus disease 2019 (COVID-19) pandemic, caused by the coronavirus-2 (SARS-CoV-2) that causes severe acute respiratory syndrome, is the world's most serious health issue. COVID-19 is currently without a precise and successful antiviral treatment. Phytochemicals provide a ray of hope for public well-being amid the pandemic, and much study is being done on them. **Materials and Methods:** Cinchona bark contains phytochemicals that have been used as antiviral agents against various viruses because they can suppress various viruses via various mechanisms of direct inhibition at the viral entry point and replication stages *via* immunomodulation potentials. Cinchona bark and its components have also been shown to have promising antiviral properties against SARS-CoV-2, according to recent data. This narrative analysis summarizes cinchona phytochemical agents, their mechanisms of action, and possible antiviral behaviours against the SARS-CoV-2 virus. **Results and Discussion:** Medicinal plants and their extracts and herbs have shown positive results in combating SARS-CoV-2 infection and could help treat COVID-19 patients as alternatives to care under phytotherapy approaches during this disastrous pandemic scenario. **Conclusion:** Finally, we presented the advantages and disadvantages of using cinchona herbal medicine during the COVID-19 pandemic, as well as some observations and suggestions.

INTRODUCTION: In Wuhan, China, a major global epidemic of coronavirus 2 that causes Severe Acute Respiratory Syndrome (SARS) started in December 2019, with 24 March 2020 records originating from 195 countries, resulting in 3.1 million deaths [1]. On March 11, 2020, the WHO declared it a pandemic and as of March 21, 2020, the viral pathogenesis and replication processes are unclear, making treatment difficult [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(3).1027-37

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(3).1027-37

No new medicines or vaccines for Covid-19 yet exist, though novel antiviral drugs are being tested. A lack of prescription medication availability has fueled the need for plant-based medicinal options, high costs, consumer expectations and alternative and folk medicine practices [3]. Herbal preparations have been used to cure a variety of diseases since ancient times and they continue to be an integral component of modern pharmacopeia.

According to the World Health Organization (WHO), conventional plant-based drugs are now used by 80% of the population of developed countries. Sadly, with the rise of mass-produced pharmaceuticals, much of mankind's arcane historical ethnobotanical knowledge has been lost [4,

[5]. Oral practices have been neglected and their present cultural significance has been ignored. For example, the Susruta Samhita and Traditional Chinese Medicine have both been collectively editorialized and debunked as pseudoscience [6]. Despite this, isolated plant constituents are already used in 25% of commonly used medications and can help to compensate for the global shortage of essential medicines. Structure of SARC-CoV2. Within a matrix protein capsid, COVID-19 are enveloped spherical particles containing single-stranded RNA and a nucleoprotein. Glycoprotein projections in the form of clubs can be found on the envelope. Any coronaviruses include the hem-agglutinin-esterase protein (HE) [7].

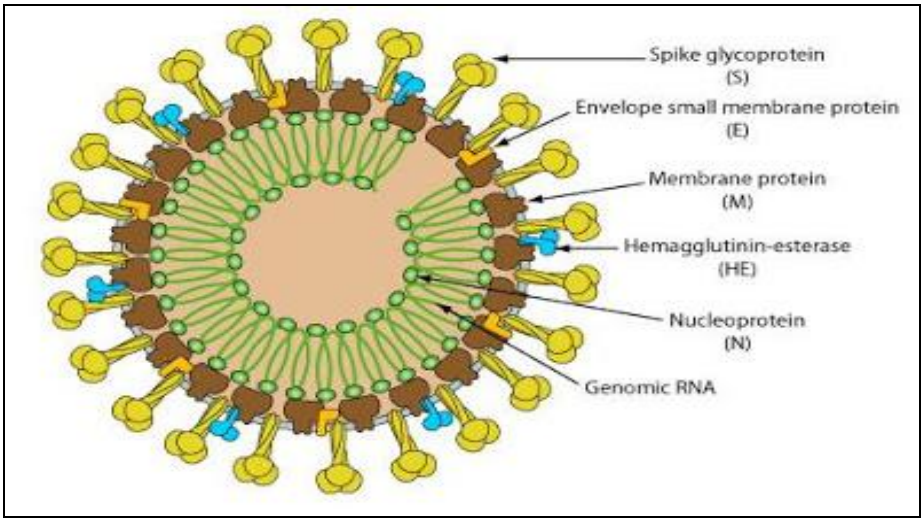

FIG. 1: STRUCTURE OF SARS-COV2 SOURCE FROM BIOWIKI. (http://ruleof6ix.fieldofscience.com/2012/09/a-new-coronavirus-should-you-care.html).

Coronaviruses have the largest genomes of any known Ribo Nucleic Acid (RNA) virus, varying from 32 to 43 percent G + C material. There are different numbers of small Open Reading Frames (ORFs) within the conserved genes and downstream of the nucleocapsid gene in different coronavirus lineages **Fig. 1**. A special N-terminal fragment inside the spike protein is one of the viral genome's distinguishing features. S, E, M, and N are the 5′–3′ order of all coronaviruses' main structural protein genes [8].

Pathogen City of SARS-CoV2: SARS-CoV2 needs a specific receptor, the Angiotensin Converting Enzyme 2 (ACE2) receptor, to enter the host cell **Fig. 2**.

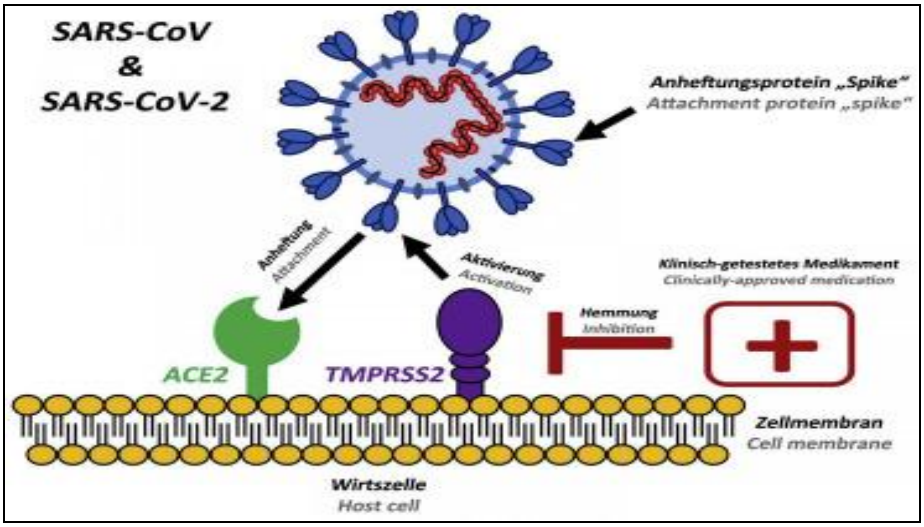

FIG. 2: ATTACHMENT OF SARS-COV [SOURCE: LEILA MOUSAVIZADEH, SORAYYA GHASEMI, GENOTYPE AND PHENOTYPE OF COVID-19: THEIR ROLES IN PATHOGENESIS. JOURNAL OF MICROBIOLOGY, IMMUNOLOGY AND, INFECTION. 2020]

The association between the virus's spike protein and the host cell's ACE2 receptor begins during the virus's internalization process [9, 10]. The activation mechanism begins when the receptor-binding domain (RBD) inside the S1 region of the virus S protein interacts with the ACE2 receptor [11]. After this encounter, the virus must reach the host cell's cytosol, which is accomplished by acid-dependent proteolytic cleavage of the spike protein by a cathepsin protease enzyme. The internalization process begins with the coronavirus fusing with the host cell membrane [12].

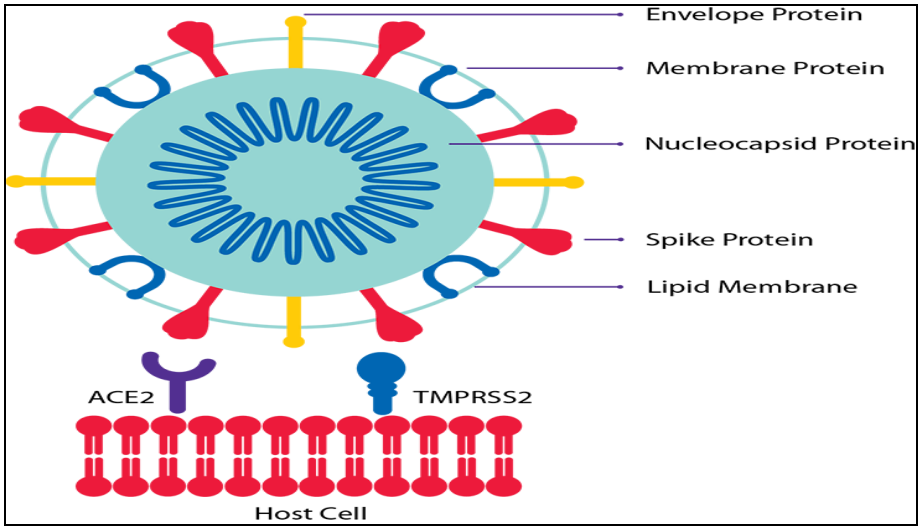

FIG. 3: THE ENTRY POINT OF SARS-COV2 IN A HOST CELL

The spike protein is cleaved in two places inside the S2 part. To distinguish the S protein's RBD and fusion domains. At S2, the peptide bond may be revealed or cleaved [13, 14]. Within acidic endosomes, the virus and the host cell typically fuse together. Few viruses can also fuse the outer membrane **Fig. 3**. The cleavage exposes the fusion peptide that incorporates into the membrane at S2. Two heptad repeats in S2 are then bound together to form an antiparallel six-helix bundle. The viral and host cell membranes fuse during bundle development, resulting in viral genome fusion and release into the cytoplasm [15].

Immunity against Infection: The opening spot of SARS-CoV-2 contamination is uncertain, also the pathogenesis of COVID-19 is being investigated. Since COVID-19 is a pulmonary condition, it usually only affects the lungs of most patients. However, psychiatric signs can worsen in certain people with comorbidities [16]. Mode of infection through direct contact with human to human. Close contact, like coughing or sneezing by an infected person or interactions with health workers and COVID-19 patients, raises the risk of infection through droplets. This disease has a 2–14-day incubation cycle, which transmits very successfully [17]. As a result of this form of infection, the disease's rate of dissemination varies, implying that the infected person will affect 2.2 and 2.6 individuals [18]. In patients treated with SARS-CoV-2, the innate immune state is uncertain [19]. According to a study, COVID-19 patients had increased neutrophils, interleukin (IL-6), and C-reactive protein (CRP) levels and a decrease in lymphocytes. How successful the innate immune system is against viruses is determined by the efficacy of the interferon (IFN) type 1 reaction. IFN has been related to viral replication, the triggering of adaptive immune responses 20, and its downstream consequences.

In COVID-19, this is how the innate immune response functions. Serological information on SARS-CoV-2 is also lacking. Nine days after the onset of COVID-19, most patients had a peak rise in immunoglobulin M (IgM), which then changed to immunoglobulin G [21]. According to another research, viral load rises during then falls in the next. On day 10, major immunoglobulin levels started and rise [22]. Several viruses may have recently triggered an evolving situation in some patients due to an immune response. The cytokine release syndrome, also known as a cytokine storm, is an emerging threat [23]. This disease develops after exposure to some influenza viruses [24]. It's even

possible that it'll show up in SARS-CoV-2 infections. According to recent findings, a subset of COVID-19 patients may suffer from cytokine release syndrome (CRS) or cytokine storm syndrome (CSS). A cytokine storm is COVID-19's second leading cause of death [25], due to an underrecognized hyperinflammatory syndrome that leads to several diseases. After virus infection, cytokine storm is a disease characterized by an active proinflammatory reaction and a loss of influence over an anti-inflammatory response [26].

When tissue is damaged, the regenerative mechanism kicks in. It will cause severe organ modifications, and their cytokines will invade the bloodstream, causing a cytokine storm leading to multiorgan failure [27]. This cytokine storm in COVID-19 viral disease is characterized by a rise in interleukin, granulocyte-colony stimulating agent, IFN-c, inducible protein, monocyte chemoattractant protein, and tumour necrosis factor (TNF) [28]. Another research found that increased level of ILand MCP-1 [29, 30]. There are rising amounts of CRS in the CSS state when taken as a whole.

The above laboratory findings match SARS and other large respiratory viruses. Infection with COVID-19 can be aided by a cytokine storm [31]. This cytokine storm may be the onset of viral sepsis and lung internal cell mass damage caused by inflammation. Complications include pneumonitis, acute respiratory distress syndrome, respiratory failure, and possibly death [32].

Cinchona Bark: In this pandemic climate, an anti-malarial treatment that left an indelible mark on those who took it is on everyone's lips; its effectiveness and advantages are fiercely debated. Some countries are using hydroxychloroquine, a synthetic modification of the "wonder drug" quinine, as an experimental therapy in the battle against COVID-19. Cinchona bark (CB) from the cinchona tree, a traditional natural source of quinine, was once used to make anti-viral chloroquine analogs, which are currently being studied against SARS-CoV-19 [33, 34]. On the other hand, the medicinal applications of quinine bark have largely been relegated to history with the emergence of modern industrial-scale drug synthesis. The theoretical application of CB as an acute anti-COVID-19 monotherapy is revisited in this article [35]. These cinchona medications' immunomodulatory auto-immune applications have popularized their use in the treatment of rheumatoid arthritis, chronic lupus, and juvenile rheumatoid arthritis [36, 37].

Both chloroquine (CQ) and hydroxychloroquine (HCQ) have shown effectiveness in slowing the development of these diseases with minimal and reversible toxicity, particularly when used for a short period of time. The tolerability of CQ/HCQ and its low cost and immunomodulatory effects means that it may be used to treat viral infections and their inflammatory response [38].

The anti-inflammatory effects of CB-derived chloroquine are also thought to temper immune hyperactivation reactions, which are common in HIV/AIDS patients [39]. This property may help regulate the cytokine storm that develops late in seriously affected patients. Quinine and CQ/HCQ have also been used for restless legs syndrome since they are thought to suppress motor endplate excitability and lengthen leg muscle latency [40].

Structure of Cinchona Bark and its Derivatives: Quinine and related alkaloids (quinidine, cinchonidine,and cinchonine) found in the bark of Cinchona species. These quinoline alkaloids are isolated in multi-ton quantities on an industrial scale. Their configurations include quinoline and quinuclidine rings and a central hydroxyl group.

The arrangement of two essential stereo-geniccenters differs between the individual alkaloids also it has been used to cure malaria for over 400 years. While newer drugs such as chloroquine (1947) and artemisinin (1970s) have increasingly replaced them, their medicinal application is restricted to strains immune to drugs, also it can treat arrhythmias. Enantioselective synthesis and process of differentiation often use Cinchona alkaloids [41]. There is yet to be a natural source for a dimeric alkaloid in this family. This,Cinchona alkaloid’sactive parts were used to create a large number of synthetic dimersindustry **Fig. 4.**

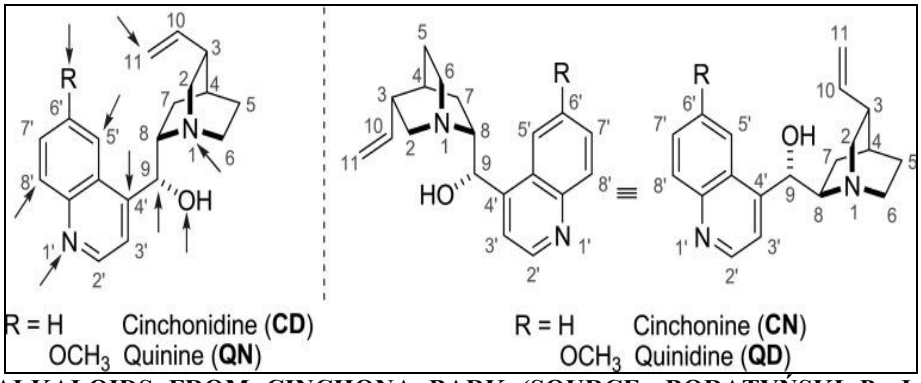

FIG. 4: MAJOR ALKALOIDS FROM CINCHONA BARK (SOURCE: BORATYŃSKI P. J. (2015). DIMERIC CINCHONA ALKALOIDS. *MOLECULAR DIVERSITY*)

Targets of Herbal Medicine: In this situation, where proper antiviral herbal therapy has not been prescribed for any infected patients, herbal medicines are widely used by many people in society. As in previous studies, a critical review of several papers from different publications relating to SARS-CoV-2 virus target molecules from plant sources was performed. At least herbal remedies have been identified as having the potential to inhibit the care of affected peoples. We also address the advantages and disadvantages of these candidates' effects [42, 43].

Cinchona against Covid 19: Cinchona sp. is a species (Chincona L., Raiatea) of Cinchona. Cinchona trees have significant impacts since a certain portion of compounds (alkaloid) contains an active molecule that cures the viral infection. Jesuit missionaries were the first to notice this beneficial influence, which spread across the globe [44]. The cinchona bark contains certain alkaloid compounds, which has been used to cure malaria for over a thousand years. Quinine works in a similar way to other synthetic drugs which contain anti-malarial activity [45-47]. Quinine compound contains sulphate is now the most widely used antibiotic.COVID-19 therapy medications are highly sought for in culture. Unacceptable Officials from the state had made remarks, anddoctors that frightened the people [48].

As a result, people searched competitively for quinine-containing medications, acts of instead of a random response, the citizens were triggered.COVID-19 has a high prevalence and mortality rate in the whole world population [49]. This segment would discuss quinine's ability to act as an immunomodulator and an antiviral agent when a virus causes an illness. Additional information will also talk about the negative consequences ofquinine on people who have COVID-19 or don't have it.

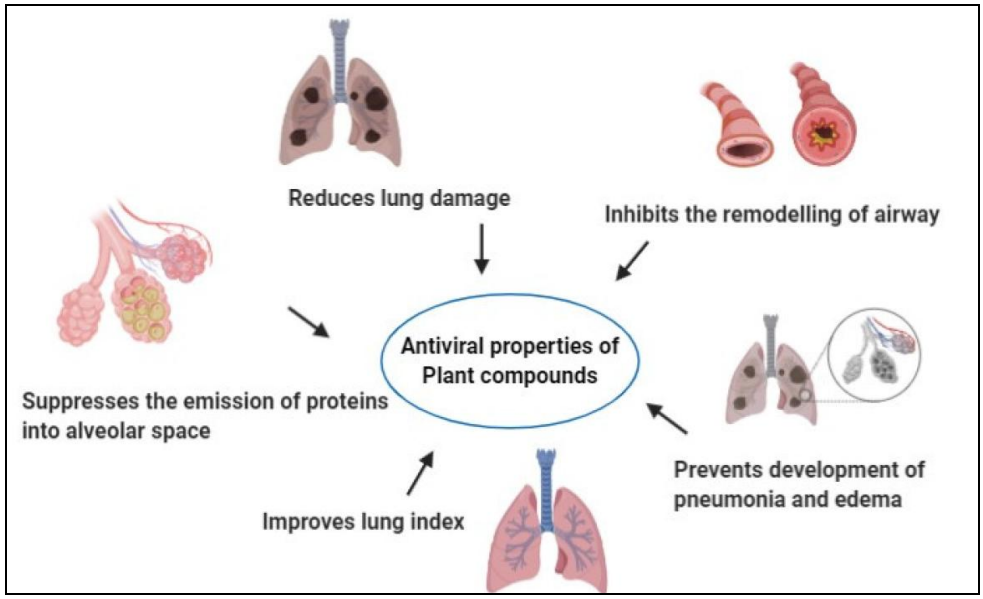

FIG. 5: ANTI-VIRAL PROPERTIES OF CINCHONA BARK

Quinine gained popularity as a substitute for the anti-malarial medication chloroquine. Malaria medications were eventually repurposed as active inhibitors of viral infection, rather than as anti-malarial drugs. A broad body of evidence indicated that many anti-malarial medications have been studied and shown to have several benefits against viral infection [50-52]. Chloroquine, for example, has been shown antiviral in case of viral infection [53-55]. When treated with azithromycin, hydroxychloroquine increases the viral load in affected patients, according to a clinical trial **Fig. 5.**

On the other hand, recentevidence, quinine and chloroquine compounds, may contain active effect and elimination properties against the SARS virus [56, 57]. Fleisher *et al.* [58] became the first to investigate the quinine effect as an anti-influenza virus infection. Furthermore, Baroni *et al.* described the antiviral effect of quinine in their study by blocking the gene expression [59-61]. Recent research consistently stated that quinine's suggested antiviral function involves viruses being killed indirectly. Previously, the effects of quinine sulphate on dengue virus-infected cells were investigated [62, 63]. The Viruses infecting host cells cause viral RNA to be released, interfering with normal protein synthesis. However, in the infected host cell, expression of RIG-I, a pathogen recognition receptor (PRR) that inhibits protein synthesis and thus blocks viral replication, increases minimally to promote the IFN-I signalling cascade rather than to elevate gene expression of IFN-stimulated genes [64-66]. In virus-infected cells, the RNase L pathway will delete ssRNA [67, 68]. Since, available data suggest that quinine inhibits and significant cytokine in deciding the seriousness of the viral infection, CSS does not occur after quinine administration in COVID-19 [69-72]. Although the cinchona tree extract does not induce CSS specifically, a systematic analysis published by Liles et al. found quinine causes a number of immune-mediated and toxic reactions [73, 74]. Quinine is rarely classified as an immunomodulatory agent but has antiviral immunostimulant and immunosuppressive properties. Quinine acts as an immunostimulator to inhibit viruses by efficiently increasing the synthesis of the well-known cytokine IFN [75].

TABLE 1: MEDICINAL USES OF CINCHONA AND ITS DERIVATIVES

S. no.	Type of uses	Compounds	Year	References
1	Anti-malarial activity	Alkaloid form	1990	77
2	Reductive amination reaction	Cinchonidine, Quinine and Quinidine	2002	78
3	Endophytic activity	Quinine, Quinidine, Cinchonidine, and Cinchonine	2003	79
4	Anti-viral for HIV (Human Immune-deficiency Virus)	Trifluoromethyl ketamines	2011	80
5	Cytostatic agents	3'-azido-3'-deoxythymidine (AZT), 10,11-didehydro Cinchona alkaloids, 9-O-propargyl ethers	2011	81
6	Antitrypanosomal, Antileishmanial, Antiplasmodial and, Cytotoxicity activity	Quinine, Quinidine, Cinchonine and Cinchonidine	2013	82
7	Antibiotics, Glutamate receptor agonists and, antagonists	Rhodium-catalyzed C-H amination and indium-catalyzed Conia-ene and phoslactomycin	2014	83
8	Cytotoxicity against cancer cell lines	Cinchonanines A-G	2014	84
9	Human butyrylcholinesterase (HBChE) activity	10,11-dibromo-10,11-dihydrocinchonidine	2014	85
10	Intramolecular spirocyclization	N,N'-disubstituted cinchona alkaloids	2014	86
11	Asymmetric synthesis of biological molecule	Dihydroxylation and aminohydroxylation ligands, and dimeric phase transfer catalysts	2015	87
12	Anti-proliferative activity of cancer cell line	1,3-dipolar Huisgen cycloaddition (click chemistry) of respective N-propargyl amides of salinomycin or monensin	2015	88
13	Molecule inhibition and Autophagy activity	Samarium diiodide	2016	89
14	Autophagy inhibitors	Oxazatwistane compound	2017	90
15	Inhibit starvation- and rapamycin-induced autophagy	Indocinchona alkaloids	2020	91

On the other hand, Quinine inhibits TNF-production and has an immunosuppressive effect. These two distinct behaviors can have a beneficial impact on COVID-19-infected individuals. However, it is not advised that healthy people take this herbal remedy regularly to avoid COVID-19 because it has the potential to produce a variety of negative side effects [76] **Table 1.**

Safety Profile of Cinchona Bark's: Even though some experts believe quinine, CQ/HCQ is essentially safe, therapeutic, and over-therapeutic levels can have severe or fatal effects. Overdosing, whether intentional or unintentional, has been attributed to severe and often lethal heart arrhythmias, with fatal poisoning being of special concern in young children [92]. There have also been reports of interactions with anti-clotting and anti-epileptic drugs [93, 94]. Dizziness, acute blindness, cardiomyopathy somnolence, suicidal ideation, and anaphylactic shock can occur with higher quinine doses, but these effects are reversible. In non-severe cases, though, most signs go away after you stop smoking [95, 96]. Aluminium-containing antacids, cholinesterase inhibitors, cimetidine, digoxin, neuromuscular disrupting agents, warfarin and other medications have also been linked to serious drug interactions.

Despite these side effects, synthetic CQ and HCQ analogues have been prescribed for more than 50 years, with reassuring acute administration protection profiles in the treatment of rheumatological diseases. Adverse CQ/HCQ side effects normally appear after several years of treatment, with macular retinopathy being the most severe of the side effects. Toxicity is often continuous rather than dose-dependent, and vision screening during treatment can help prevent irreversible retinal injury [97, 98]. According to another report, 500 mg of high-dose CQ a day for treating Rheumatology disorders whilst breastfeeding had a reassuring ocular defense profile [99]. Furthermore, Savarino and colleagues concluded that CQ/HCQ administration has a low risk/benefit ratio and a limited and preventable toxicity profile, especially in life-threatening conditions such as SARS and AIDS [100, 101].

CONCLUSION: Based on the previous description, we infer that phytoremedies may have the capacity to secrete and regulate the cytokines that can interact and alter the internal molecular pathway relevant to the immune system. Herbal agents may be helpful in the war against COVID-19. Finally, patients should be advised that using a supplement substance to avoid a specific viral disease without the specific guidance of a clinician is still not recommended. A recommendation for the clinician is that, even though the patient is well, these medicines should be done with caution. This is because there has been a lot of conflicting information about these medicines. Thus, there's a chance that these therapies are linked to the induction of negative side effects. Furthermore, no preclinical or clinical trials of these herbal agents for COVID-19 have been conducted, necessitating further testing.

ACKNOWLEDGMENT: We would like to thank the Head of the Department, Department of Life Sciences, Christ (Deemed to be University), Bangalore, Karnataka, India, for providing us with the opportunity and requirements needed for the accomplishment of the research project. We also appreciate all study participants for volunteering to partake in the study.

Funding Source: Funding has not been received for this study.

CONFLICTS OF INTERESTS: Present study does not contain any conflict of interest.

REFERENCES:

1. Zhu N, Zhang D and Wang W: A Novel Coronavirus from Patients with Pneumonia in China 2019. N Engl J Med. 2020; 382(8): 727-733. doi:10.1056/NEJMoa2001017
2. Perlman S: Another Decade, another Coronavirus. N Engl J Med 2020; 382(8): 760-762.
3. Li Q, Guan X and Wu P: Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020; 382(13): 1199-1207.
4. Jiang S, Xia S, Ying T and Lu L: A novel coronavirus (2019-nCoV) causing pneumonia-associated respiratory syndrome. Cell Mol Immunol 2020; 17(5): 554.
5. Jiang S, Xia S, Ying T and Lu L: A novel coronavirus (2019-nCoV) causing pneumonia-associated respiratory syndrome. Cell Mol Immunol 2020; 17(5): 554. doi:10.1038/s41423-020-0372-4
6. Ogal M, Johnston SL, Klein P and Schoop R: Echinacea reduces antibiotic usage in children through respiratory tract infection prevention: a randomized, blinded, controlled clinical trial. Eur J Med Res 2021; 26(1): 33. Published 2021 Apr 8. doi:10.1186/s40001-021-00499-6
7. de Haan CA, Kuo L, Masters PS, Vennema H and Rottier PJ: Coronavirus particle assembly: primary structure

requirements of the membrane protein. J Virol 1998; 72(8): 6838-6850. doi:10.1128/JVI.72.8.6838-6850.1998
8. Woo PC, Huang Y, Lau SK and Yuen KY: Coronavirus genomics and bioinformatics analysis. Viruses. 2010; 2(8): 1804-1820. doi:10.3390/v2081803
9. Ge XY, Li JL and Yang XL: Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013; 503(7477): 535-538. doi:10.1038/nature12711
10. Liu L, Fang Q and Deng F: Natural mutations in the receptor binding domain of spike glycoprotein determine the reactivity of cross-neutralization between palm civet coronavirus and severe acute respiratory syndrome coronavirus. J Virol 2007; 81(9): 4694-4700. doi:10.1128/JVI.02389-06
11. Li W, Moore MJ and Vasilieva N: Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426(6965): 450-454. doi:10.1038/nature02145
12. Li W, Zhang C and Sui J: Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J 2005; 24(8): 1634-1643. doi:10.1038/sj.emboj.7600640
13. Zhao L, Jha BK and Wu A: Antagonism of the interferon-induced OAS-RNase L pathway by murine coronavirus ns2 protein is required for virus replication and liver pathology. Cell Host Microbe 2012; 11(6): 607-616. doi:10.1016/j.chom.2012.04.011
14. Bárcena M, Oostergetel GT and Bartelink W: Cryo-electron tomography of mouse hepatitis virus: Insights into the structure of the coronavirion. Proc Natl Acad Sci USA 2009; 106(2): 582-587. doi:10.1073/pnas.0805270106
15. Neuman BW, Adair BD and Yoshioka C: Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. J Virol. 2006; 80(16): 7918-7928. doi:10.1128/JVI.00645-06
16. Esmaeilzadeh A, Jafari D, Tahmasebi S, Elahi R and Khosh E: Immune-Based Therapy for COVID-19. Adv Exp Med Biol 2021; 1318: 449-468. doi:10.1007/978-3-030-63761-3_26
17. Rezaei N, Ashkevarian S and Fathi MK: Introduction on Coronavirus Disease (COVID-19) Pandemic: The Global Challenge. Adv Exp Med Biol 2021; 1318: 1-22. doi:10.1007/978-3-030-63761-3_1
18. Nagy A and Alhatlani B: An overview of current COVID-19 vaccine platforms. Comput Struct Biotechnol J 2021; 19: 2508-2517. doi:10.1016/j.csbj.2021.04.061
19. Wu Z and McGoogan JM: Characteristics of and 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 2020; 323(13): 1239-1242. doi:10.1001/jama.2020.2648
20. Chan JF, Yuan S and Kok KH: A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395(10223): 514-523. doi:10.1016/S0140-6736(20)30154-9
21. Mishra R and Banerjea AC: SARS-CoV-2 Spike Targets USP33-IRF9 Axis *via* Exosomal miR-148a to Activate Human Microglia. Front Immunol 2021; 12: 656700. Published 2021 Apr 14. doi:10.3389/fimmu.2021.656700
22. Park HH, Kim H and Lee HS: PEGylated nanoparticle albumin-bound steroidal ginsenoside derivatives ameliorate SARS-CoV-2-mediated hyper-inflammatory responses. Biomaterials 2021; 273: 120827. doi:10.1016/j.biomaterials.2021.120827
23. Huang C, Wang Y and Li X: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;. Lancet 2020; 395(10223): 497-506. doi:10.1016/S0140-6736(20)30183-5
24. Ritchie AI and Singanayagam A: Immunosuppression for hyperinflammation in COVID-19: a double-edged sword. Lancet 2020; 395(10230): 1111. doi:10.1016/S0140-6736(20)30691-7
25. Tveito K: Cytokine storms in COVID-19 cases. Cytokinstormerved covid-19. Tidsskr Nor Laegeforen. 2020; 140: 10.4045/tidsskr.20.0239. Published 2020 Mar 23. doi:10.4045/tidsskr.20.0239
26. Mazloom R: Feasibility of Therapeutic Effects of the Cholinergic Anti-Inflammatory Pathway on COVID-19 Symptoms. J Neuroimmune Pharmacol 2020; 15(2): 165-166. doi:10.1007/s11481-020-09919-6
27. Lin CH, Chen CH and Hong SY: Comparison of severe pediatric complicated influenza patients with and without neurological involvement. Medicine (Baltimore). 2021; 100(17): 25716. doi:10.1097/MD.0000000000025716
28. Leverenz DL and Tarrant TK: Is the HScore useful in COVID-19. Lancet. 2020; 395(10236): e83. doi:10.1016/S0140-6736(20)31057-6
29. Giannini M, Ohana M, Nespola B, Zanframundo G, Geny B and Meyer A: Similarities between COVID-19 and anti-MDA5 syndrome: what can we learn for better care. Eur Respir J 2020; 56(3): 2001618. Published 2020 Sep 24. doi:10.1183/13993003.01618-2020
30. Schultheiß C, Paschold L and Simnica D: Next-Generation Sequencing of T and B Cell Receptor Repertoires from COVID-19 Patients Showed Signatures Associated with Severity of Disease. Immunity 2020; 53(2): 442-455.e4. doi:10.1016/j.immuni.2020.06.024
31. Aspatwar A, Gong W, Wang S, Wu X and Parkkila S: Tuberculosis vaccine BCG: the magical effect of the old vaccine in the fight against the COVID-19 pandemic. Int Rev Immunol. 2022; 41(2): 283-296. doi:10.1080/08830185.2021.1922685
32. Dezfuli NK, Adcock IM, Montazami N, Mortaz E and Velayati A: Update on Immunology of COVID-19 Disease and Potential Strategy for Controlling. Tanaffos 2020; 19(4): 274-290.
33. NagoorMeeran MF, Javed H and Sharma C: Can Echinacea be a potential candidate to target immunity, inflammation, and infection - The trinity of coronavirus disease 2019. Heliyon. 2021; 7(2): 05990.
34. Sytar O, Brestic M and Hajihashemi S: COVID-19 Prophylaxis Efforts Based on Natural Antiviral Plant Extracts and Their Compounds. Molecules. 2021; 26(3): 727. Published 2021 Jan 30. doi:10.3390/molecules26030727
35. Weishaupt R, Bächler A, Feldhaus S, Lang G, Klein P and Schoop R: Safety and Dose-Dependent Effects of Echinacea for the Treatment of Acute Cold Episodes in Children: A Multicenter, Randomized, Open-Label Clinical Trial. Children (Basel) 2020; 7(12): 292. Published 2020 Dec 15. doi:10.3390/children7120292
36. Große M, Ruetalo N and Layer M: Quinine Inhibits Infection of Human Cell Lines with SARS-CoV-2. Viruses 2021; 13(4): 647. Published 2021 Apr 9. doi:10.3390/v13040647
37. Das S, Ramachandran AK, Birangal SR, Akbar S, Ahmed B and Joseph A: The controversial therapeutic journey of chloroquine and hydroxychloroquine in the battle against SARS-CoV-2: A comprehensive review. Med Drug

Discov 2021; 10: 100085. doi:10.1016/j.medidd.2021.100085
38. Osmani Z, Schrama TJ and Zacouris-Verweij W: Hydroxychloroquine treatment in European patients with lupus erythematosus: dosing, retinopathy screening and adherence. Lupus Sci Med 2021; 8(1): 000478. doi:10.1136/lupus-2021-000478
39. van Welzen BJ, Oomen PGA, Hoepelman AIM. Dual Antiretroviral Therapy-All Quiet Beneath the Surface?. Front Immunol 2021; 12: 637910. Published 2021 Feb 12. doi:10.3389/fimmu.2021.637910
40. Lu L, Wang J, Yang Q, Xie X and Huang Y: The role of CD38 in HIV infection. AIDS Res Ther 2021; 18(1): 11. Published 2021 Apr 5. doi:10.1186/s12981-021-00330-6
41. Song CE: Cinchona alkaloids in synthesis and catalysis. Weinheim: Wiley 2019
42. Ang L, Lee HW, Kim A, Lee JA, Zhang J and Lee MS: Herbal medicine for treatment of children diagnosed with COVID-19: A review of guidelines. Complement Ther Clin Pract 2020; 39: 101174. doi:10.1016/j.ctcp.2020.101174
43. Li Y, Liu X and Guo L: Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: protocol for a systematic review and meta-analysis. Syst Rev 2020; 9(1): 75. Published 2020 Apr 8. doi:10.1186/s13643-020-01343-4
44. Aerts RJ, de Waal A, Pennings EJ and Verpoorte R: The distribution of strictosidine-synthase activity and alkaloids in Cinchona plants. Planta 1991; 183(4): 536-541. doi:10.1007/BF00194275
45. Andersson L and Antonelli A: Phylogeny of the tribe Cinchoneae (Rubiaceae), its position in Cinchonoideae, and description of a new genus, Ciliosemina. Taxon 2005; 54: 17–28.
46. Shah S, Das S, Jain A, Misra DP and Negi VS: A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). Int J Rheum Dis 2020; 23(5): 613-619. doi:10.1111/1756-185X.13842
47. de Barros CM, Almeida CAF and Pereira B: COVID-19 Pandemic - A Narrative Review of the Potential Roles of Chloroquine and Hydroxychloroquine. Pain Physician 2020; 23(4): 351-366.
48. Wax RS and Christian MD: Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Directives concrètes à l'intention des équipes de soinsintensifs et d'anesthésiologieprenantsoin de patients atteints du coronavirus 2019-nCoV. Can J Anaesth 2020; 67(5): 568-576. doi:10.1007/s12630-020-01591-x
49. Han Q, Lin Q, Jin S and You L: Coronavirus 2019-nCoV: A brief perspective from the front line. J Infect. 2020; 80(4): 373-377. doi:10.1016/j.jinf.2020.02.010
50. Haynes RK, Cheu KW, N'Da D, Coghi P and Monti D: Considerations on the mechanism of action of artemisinin anti-malarials: part 1--the 'carbon radical' and 'heme' hypotheses. Infect Disord Drug Targets 2013; 13(4): 217-277. doi:10.2174/18715265133666131129155708
51. Al-Bari MAA: Targeting endosomal acidification by chloroquineanalogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res Perspect 2017; 5(1): 00293. Published 2017 Jan 23. doi:10.1002/prp2.293
52. Benelli G and Mehlhorn H: Declining malaria, rising of dengue and Zika virus: insights for mosquito vector control. Parasitol Res. 2016; 115(5):1747-1754. doi:10.1007/s00436-016-4971-z
53. Kuhn JH, Li W, Radoshitzky SR, Choe H and Farzan M: Severe acute respiratory syndrome coronavirus entry as a target of antiviral therapies. Antivir Ther 2007; 12(4): 639-650.
54. Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M and Taguchi F: Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. J Virol 2010; 84(24): 12658-12664. doi:10.1128/JVI.01542-10
55. Han DP, Penn-Nicholson A and Cho MW: Identification of critical determinants on ACE2 for SARS-CoV entry and development of a potent entry inhibitor. Virology 2006; 350(1): 15-25. doi:10.1016/j.virol.2006.01.029
56. Duška F, Waldauf P and Halačová M: Azithromycin added to hydroxychloroquine for patients admitted to intensive care due to coronavirus disease 2019 (COVID-19)-protocol of randomised controlled trial AZIQUINE-ICU. Trials 2020; 21(1): 631. Published 2020 Jul 8. doi:10.1186/s13063-020-04566-x
57. Panda PK, Bandyopadhyay A and Singh BC: Safety and efficacy of antiviral combination therapy in symptomatic patients of Covid-19 infection - a randomised controlled trial (SEV-COVID Trial): A structured summary of a study protocol for a randomized controlled trial. Trials 2020; 21(1): 866. Published 2020 Oct 20. doi:10.1186/s13063-020-04774-5
58. Fleisher MS. The effect of various dyes *in-vitro* and *in-vivo* upon influenza virus infection in mice. J Immunol 1949; 62(2): 245-255.
59. Jiang J, Fisher EM and Murasko DM: CD8 T cell responses to influenza virus infection in aged mice. Ageing Res Rev 2011; 10(4): 422-427. doi:10.1016/j.arr.2011.02.001
60. Wolf R, Baroni A and Greco R: Quinine sulfate and HSV replication. Dermatol Online J 2003; 9(3): 3.
61. Souza TM, Abrantes JL, de A Epifanio R, LeiteFontes CF and Frugulhetti IC: The alkaloid 4-methylaaptamine isolated from the sponge Aaptosaaptos impairs Herpes simplex virus type 1 penetration and immediate-early protein synthesis. Planta Med 2007; 73(3): 200-205. doi:10.1055/s-2007-967109
62. Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR and Abubakar S: Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virol J. 2011; 8: 560. Published 2011 Dec 28. doi:10.1186/1743-422X-8-560
63. Chew MF, Tham HW, Rajik M and Sharifah SH: Anti-dengue virus serotype 2 activity and mode of action of a novel peptide. J Appl Microbiol 2015; 119(4): 1170-1180. doi:10.1111/jam.12921
64. Xue M, Fu F and Ma Y: The PERK Arm of the Unfolded Protein Response Negatively Regulates Transmissible Gastroenteritis Virus Replication by Suppressing Protein Translation and Promoting Type I Interferon Production. J Virol 2018; 92(15): e00431-18. Published 2018 Jul 17. doi:10.1128/JVI.00431-18
65. Liu Y, Wang M and Cheng A: The role of host eIF2α in viral infection. Virol J. 2020; 17(1): 112. Published 2020 Jul 23. doi:10.1186/s12985-020-01362-6
66. Dong HJ, Zhang R, Kuang Y and Wang XJ: Selective regulation in ribosome biogenesis and protein production for efficient viral translation. Arch Microbiol 2021; 203(3): 1021-1032. doi:10.1007/s00203-020-02094-5
67. Samuel CE: Antiviral actions of interferons. Clin Microbiol Rev 2001; 14(4): 778-809. doi:10.1128/CMR.14.4.778-809.2001

68. Boo KH and Yang JS: Intrinsic cellular defenses against virus infection by antiviral type I interferon. Yonsei Med J 2010; 51(1): 9-17. doi:10.3349/ymj.2010.51.1.9
69. Gonçalves de Moraes VL, Singer M, Vargaftig BB and Chignard M: Effects of rolipram on cyclic AMP levels in alveolar macrophages and lipopolysaccharide-induced inflammation in mouse lung. Br J Pharmacol 1998; 123(4): 631-636. doi:10.1038/sj.bjp.0701649
70. Skwor TA, Cho H, Cassidy C, Yoshimura T and McMurray DN: Recombinant guinea pig CCL5 (RANTES) differentially modulates cytokine production in alveolar and peritoneal macrophages. J Leukoc Biol 2004; 76(6): 1229-1239. doi:10.1189/jlb.0704414
71. Newton PN, Angus BJ and Chierakul W: Randomized comparison of artesunate and quinine in the treatment of severe falciparum malaria. Clin Infect Dis 2003; 37(1): 7-16. doi:10.1086/375059
72. Noedl H, Krudsood S and Chalermratana K: Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated Plasmodium falciparum malaria in adults: a randomized, phase 2 clinical trial in Thailand. Clin Infect Dis 2006; 43(10): 1264-1271. doi:10.1086/508175
73. Page EE, Little DJ, Vesely SK and George JN: Quinine-Induced Thrombotic Microangiopathy: A Report of 19 Patients. Am J Kidney Dis 2017; 70(5): 686-695. doi:10.1053/j.ajkd.2017.05.023
74. Knower MT, Bowton DL, Owen J and Dunagan DP: Quinine-induced disseminated intravascular coagulation: case report and review of the literature. Intensive Care Med 2003; 29(6): 1007-1011.
75. Howard MA, Hibbard AB, Terrell DR, Medina PJ, Vesely SK and George JN: Quinine allergy causing acute severe systemic illness: report of 4 patients manifesting multiple hematologic, renal, and hepatic abnormalities. Proc (Bayl Univ Med Cent) 2003; 16(1): 21-26. doi:10.1080/08998280.2003.11927884
76. Lim AK, Ho L and Levidiotis V: Quinine-induced renal failure as a result of rhabdomyolysis, haemolytic uraemic syndrome and disseminated intravascular coagulation. Intern Med J 2006; 36(7): 465-467.
77. Laraia L, Ohsawa K and Konstantinidis G: Discovery of Novel Cinchona-Alkaloid-Inspired Oxazatwistane Autophagy Inhibitors. Angew ChemInt Ed Engl. 2017; 56(8): 2145-2150. doi:10.1002/anie.201611670
78. Foley DJ, Zinken S and Corkery D: Phenotyping Reveals Targets of a Pseudo-Natural-Product Autophagy Inhibitor. AngewChemInt Ed Engl 2020; 59(30): 12470-12476. doi:10.1002/anie.202000364
79. Baraniak D, Kacprzak K and Celewicz L: Synthesis of 3'-azido-3'-deoxythymidine (AZT)--Cinchona alkaloid conjugates via click chemistry: Toward novel fluorescent markers and cytostatic agents. Bioorg Med Chem Lett 2011; 21(2): 723-726. doi:10.1016/j.bmcl.2010.11.127
80. Schröder P, Bauer JO, Strohmann C, Kumar K and Waldmann H: Synthesis of an Iridoid-Inspired Compound Collection and Discovery of Autophagy Inhibitors. J Org Chem 2016; 81(21): 10242-10255.
81. Boratyński PJ: Dimeric Cinchona alkaloids. Mol Divers. 2015; 19(2): 385-422. doi:10.1007/s11030-014-9563-1
82. Hatakeyama S: Total synthesis of biologically active natural products based on highly selective synthetic methodologies. Chem Pharm Bull (Tokyo) 2014; 62(11): 1045-1061. doi:10.1248/cpb.c14-00474
83. Cheng GG, Cai XH and Zhang BH: Cinchona alkaloids from Cinchona succirubra and Cinchona ledgeriana. Planta Med 2014; 80(2-3): 223-230. doi:10.1055/s-0033-1360279
84. Karlsson D, Fallarero A and Shinde P: Chemical modifications of cinchona alkaloids lead to enhanced inhibition of human butyrylcholinesterase. Nat Prod Commun 2014; 9(4): 455-458.
85. Shibuya H, Kitamura C and Maehara S: Transformation of Cinchona alkaloids into 1-N-oxide derivatives by endophyticXylariasp isolated from Cinchona pubescens. Chem Pharm Bull (Tokyo) 2003; 51(1): 71-74. doi:10.1248/cpb.51.71
86. Xie H, Zhang Y, Zhang S, Chen X and Wang W: Bifunctional Cinchona alkaloid thioureacatalyzed highly efficient, enantioselectiveaza-Henry reaction of cyclic trifluoromethylketimines: synthesis of anti-HIV drug DPC 083. AngewChemInt Ed Engl 2011; 50(49): 11773-11776. doi:10.1002/anie.201105970
87. Xiang B, Belyk KM, Reamer RA and Yasuda N: Discovery and application of doubly quaternized cinchona-alkaloid-based phase-transfer catalysts. AngewChemInt Ed Engl 2014; 53(32): 8375-8378. doi:10.1002/anie.201404084
88. Leverrier A, Bero J, Frédérich M, Quetin-Leclercq J and Palermo J: Antiparasitic hybrids of Cinchona alkaloids and bile acids. Eur J Med Chem 2013; 66: 355-363. doi:10.1016/j.ejmech.2013.06.004
89. Lambers M, Beijer FH, Padron JM, Toth I and de Vries JG: Highly selective hydroformylation of the cinchona alkaloids. J Org Chem 2002; 67(14): 5022-5024. doi:10.1021/jo0255173
90. Wesche DL and Black J: A comparison of the anti-malarial activity of the cinchona alkaloids against Plasmodium falciparum in vitro. J Trop Med Hyg 1990; 93(3): 153-159.
91. Skiera I, Antoszczak M and Trynda J: Antiproliferative Activity of Polyether Antibiotic--Cinchona Alkaloid Conjugates Obtained via Click Chemistry. Chem Biol Drug Des 2015; 86(4): 911-917. doi:10.1111/cbdd.12523
92. Mvango S, Matshe WMR, Balogun AO, Pilcher LA and Balogun MO: Nanomedicines for Malaria Chemotherapy: Encapsulation vs. Polymer Therapeutics. Pharm Res 2018; 35(12): 237. Published 2018 Oct 15. doi:10.1007/s11095-018-2517-z
93. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA and Dondorp AM: Malaria. Lancet 2014; 383(9918): 723-735. doi:10.1016/S0140-6736(13)60024-0
94. Plewes K, Leopold SJ, Kingston HWF and Dondorp AM: Malaria: What's New in the Management of Malaria. Infect Dis Clin North Am 2019; 33(1): 39-60. doi:10.1016/j.idc.2018.10.002
95. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y and Forthal DN: Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs 2020; 80(13): 1267-1292. doi:10.1007/s40265-020-01367-z
96. Hergesheimer R, Lanznaster D and Vourc'h P: Advances in disease-modifying pharmacotherapies for the treatment of amyotrophic lateral sclerosis. Expert Opin Pharmacother 2020; 21(9): 1103-1110. doi:10.1080/14656566.2020.1746270
97. El Rhazi K and Adarmouch L: Ethical issues related to the hydroxychloroquine treatment prescription for Covid-19. Ethics Med Public Health 2020; 14: 100547.
98. Sarma P, Kaur H and Kumar H: Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis. J Med Virol 2020; 92(7): 776-785.
99. Machiels JD, Bleeker-Rovers CP and Ter Heine R: Reply to Gautret: hydroxychloroquinesulfate and azithromycin for COVID-19: what is the evidence and what are the

risks. Int J Antimicrob Agents 2020; 56(1): 106056. doi:10.1016/j.ijantimicag.2020.106056.

100. Ding HJ, Denniston AK, Rao VK and Gordon C: Hydroxychloroquine-related retinal toxicity. Rheumatology (Oxford). 2016; 55(6): 957-967.

101. Dutta D, Sharma M and Sharma R: Short-term Hydroxychloroquine in COVID-19 Infection in People with or Without Metabolic Syndrome - Clearing Safety Issues and Good Clinical Practice. Eur Endocrinol 2020; 16(2): 109-112. doi:10.17925/EE.2020.16.2.109.

How to cite this article:
Pappuswamy M, Meyyazhagan A and Chaudhary A: Cinchona exhibits candidates as a complementary antiviral activity for SARS-Cov-2: a narrative review. Int J Pharm Sci & Res 2023; 14(3): 1027-37. doi: 10.13040/IJPSR.0975-8232.14(3). 1027-37.