MEDICINAL PLANTS AND VACCINATIONS USED AGAINST COVID-19: A COMPREHENSIVE REVIEW

Haidar Ali[1], Amir Muhammad Khan[1*], Anwar Zaman[2], Mehboob Ali[8], Aneeba Malik[3], Ashfaq Ahmad[4], Zainab Jan[5], Shiza Malik[6], Navid Iqbal[1], Javaid Hasssan[2], Kainat Ahmad[7], Yaser Ud Din[8], KINKPE Lionel[9], Nasir Khan[10], and Ihtesham Ul Haq[1]

DOI: 10.28941/pjwsr.v28i4.1105

ABSTRACT

The newly emerged severe acute respiratory syndrome corona virus-2 (SARS-CoV-2), the causative agent of corona virus disease 2019 (COVID-19), has deteriorated the global order economically, socially and politically. As an emergency of global concern, the disease continuously spread havoc with its dreadful health manifestations with no regard for any race, religion and region. The mortality rates in different countries are surprisingly variable and there is debate about population-wise differential response to virus. Different countries have imposed lock-down to reduce the spread of virus; however, the positive outcomes of lock-down in terms of reducing mortality rate and transmission of virus are still questioned. Further, public accusations and debate of world powers regarding the origin of virus has created regional hate sentiments and political chaos which could result is serious repercussions following miscalculation of actual facts. Scientific communities are struggling to cope with the disease by developing potential vaccines against the S protein of SARS-CoV-2 and were testing the already marketed drugs against this coronavirus. Therefore, several medicinal plants and various vaccinations have been used against Covid-19. This review highlights the origin, virulence, vaccination but most importantly the plants extracts used against the causative agent of COVID-19.

Keywords. SARS-CoV-2, COVID-19, Plants metabolites, Virulence, Vaccination.

Citation: Ali. H., A. M. Khan, A. Zaman, M. Ali, A. Malik, A. Ahmad, Z. Jan, S. Malik, N. Iqbal, J. Hassan, K. Ahmad, Y. U. Din, K. Lionel, N. Khan and I. U. Haq. 2022. Medicinal plants and vaccinations used against covid-19: a comprehensive review. Pak. J. Weed Sci. Res., 28(4): 435-446.

[1] *Institute of Biotechnology & Genetic Engineering, The University of Agriculture, Peshawar, Pakistan*

[*] *Correspondence to:* amirmuhammad@aup.edu.pk

[2] *Department of Soil and Environmental Science, The University of Agriculture, Peshawar, Pakistan*

[3] *Department of Zoology, University of Swat, Swat, Pakistan*

[4] *University of Warwick, Coventry, CV 7AL, United Kingdom*

[5] *Department of Bioinformatics, Hazara University, KP, Pakistan*

[6] *Atta-ur-rahman School of Applied Biosciences, National University of Science & Technology, (ASAB NUST), Islamabad, Pakistan*

[7] *National University of Science and Technology, Islamabad, Pakistan*

[8] *Khyber Medical University, Peshawar, Pakistan*

[9] *College of Veterinary Science, the University of Agriculture, Peshawar, Pakistan.*

[10] *Agriculture Research Institute, Mingora, Swat, Pakistan*

INTRODUCTION

Corona virus disease 2019 (COVID-19) is an infectious disease caused by a previously unidentified coronavirus introduced to humans for the first time in China. In the last two decades, several other viral outbreaks such as SARS-CoV in China (in 2002), H1N1 influenza in Mexico (in 2009), and the Middle-East respiratory syndrome coronavirus (MERS-CoV) in Saudi-Arabia (in 2012) were identified in civet cats, pigs, and dromedary camels, respectively (Hu et al., 2015). In December 2019, an outbreak began in Wuhan (Hubei province), China, was detected in a group of patients having initial sign and symptoms of pneumonia, this new coronavirus called 2019-nCoV or severe acute respiratory syndrome corona virus-2 (SARS-CoV-2), it was identified as the cause of COVID-19 (Mackay and Arden, 2015). SARS-CoV-2 stands seventh among coronaviruses family that infects humans and unlike other human coronaviruses it is affects the lower respiratory tract and can cause a serious disease named acute respiratory distress syndromes (ARDS) (Chan et al., 2015). The epidemics caused by MERS-CoV, SARS-CoV and SARS-CoV-2 are all linked to wild animal markets [8]. SARS-CoV-2 is enveloped; single positive-stranded RNA viruses (+ssRNA) due to presence of spike (S) glycoproteins on the envelope (nucleocapsid) it appears like a crown under electron microscope. They have elliptic or round or often pleomorphic-form, and a diameter of approximately 80–160 nm (Latif and Mukaratirwa, 2020). Based on phylogenetic and taxonomy, it belongs to SARS-CoV species and *Betacoronavirus* genus [9, 10]. Full genomic length of this unique coronavirus is approximately 30 kb (encoding 9860 amino acids) (Frutos et al., 2021). Viral genome sequence shows 89% nucleotides identity with bat SARS-like-CoVZXC21 and 85% with that of human SARS-CoV, suggesting its zoonotic origin from bats as a natural host. Population of generally all age groups and genders are vulnerable to SARS-CoV-2 (Ge et al., 2015). This virus has relative high transmissibility with basic reproduction rate (R0) of 2.47-5.7 as compared to SARS (R0 2) and flu H1N1 (R0 1.3). However, the comparative mortality rate is quite lower than SARS-CoV and MERS-CoV, having 17% and 34% fatality rate, respectively (Graham et al., 2013). Human-to-human contact is main route of transmission, in addition to wild animal reservoirs, coughing and sneezing, faecal-oral route, stool, gastrointestinal tract, saliva, urine, and nosocomial transmission (Zhou et al., 2021). No case of vertical transmission has been reported so far. The incubation period ranges from 2 to 14 days with median latency of 5 days, which is similar to other SARS-CoVs (5 days) and relatively less than MERS (7 days). Clinical features vary from simple respiratory infection to septic-shock. The most common symptoms are defined as fever, dry cough, dyspnoea, myalgia and fatigue, while muscle ache, headache, confusion, rhinorrhoea, sore throat, sputum production, diarrhoea, chest-pain, nausea and vomiting are rare (Poudel et al., 2020). The complications of COVID-19 seen included ARDS, shock, acute heart, lung and kidney injury, neurological manifestation, RNAaemia and multiple organ failure (Khan et al., 2020).

Origination and history of SARS-CoV-2

Many scientists reported that all early incidents of COVID-19 were associated to the Huanan market located in Wuhan city of China, where an animal source was present (Reperant and Osterhaus, 2017). As the SARS-CoV-2 is genetically identical to bat SARS-CoV-like coronaviruses (Tsang, 2014), it is expected that bats act as host (reservoir) for its ancestor. It has been reported that RaTG13, a virus belonging to *Rhinolophus affinis* bat1 shows a similar genomic sequence (~96%) with SARS-CoV-2, but its S protein diverges near receptor binding domain (RBD), which indicates it never engage probably to human ACE2 (angiotensin converting-enzyme-2; S protein receptor) (Parihar et al., 2021). A recent report showed that Malayan pangolins (Manis javanica) were illicitly brought into the Guangdong province that contained coronaviruses, which is identical to novel SARS-CoV-2. The SARS-CoV-2 is closely resembled with RaTG13 bat virus at genomic level, while pangolin coronaviruses show solid resemblance to SARS-CoV-2 at RBD level, containing all six important RBD

residues (Dhama et al., 2020). These evidences obviously reveal that the engagement of SARS-CoV-2 S protein to human like ACE2 is the outcome of natural-selection.

Possible treatments

Initially, there were multiple antiviral medicines for the prevention and treatment of COVID-19. Based upon those, the focus was merely on treating the complications associated with this disease such as pneumonia, acute respiratory failure, etc. Several antiviral drugs such as chloroquine (CQ) and hydroxychloroquine (HCQ) (antimalarial), remdesivir (used against Ebola), lopinavir and ritonavir (anti-human immunodeficiency virus; HIV) and favipiravir have shown promising results (Lei et al., 2020). However, various approved vaccines have brought a paradigm shift in the pioneer-medication agents. To name, Pfizer, BioNTech, Moderna and Sino-Vac COVID-19 vaccines are the leading ones. Besides these 275 vaccines are in development, 106 are in clinical testing, 9 different platforms and 24 in use.

Plants extracts used against COVID-19 and associated impacts

Alkaloids are plants secondary metabolites with a wide range of biological functions, particularly antimalarial activity and many researchers have been reported for the COVID-19 treatments. Quinine, an aminoquinoline alkaloid discovered by Pelletier and Caventou in the bark of Cinchona species (Rubiaceae) in 1820, is now used as one of the most efficient antimalarial treatments (Greenwood et al., 2005). The anti-COVID-19 activity of Cinchona bark (CB) may be similar to that of the synthetic CQ/HCQ, but it also has the same risk of serious medication interactions and potentially fatal side effects as its counterparts. Other issues include problems with herbal quality control and lack of knowledge with prescriber doses (Inklebarger et al., 2020).

Chloroquine (CQ) and hydroxychloroquine (HCQ) (antimalarial)

CQ and HCQ have been branded as possible "game-changers" in the well-known print media for COVID-19 [63]. CQ was first time manufactured in 1934 and had been ordained broadly for the prevention and cure aid of malaria and autoimmune disease such as system lupus erythematosus and rheumatoid arthritis (Erickson et al., 2020). Additionally, both agents have also shown an effective therapeutic and immune-modulatory effect against broad range of other diseases such as HIV, amebiasis, antiphospholipid syndrome and cancer (Pereira, 2020). The active mechanism of both CQ and HCQ against SARS-CoV-2 is yet to be entirely clarified. CQ was initially underlined during 2002-2003 SARS-CoV epidemic (Tripathy et al., 2020). On the basis of studying initial SARS-CoV, it is thought that SARS-CoV-2 arrives inside the cells via binding to receptor named ACE2, and that CQ may stop the virus from binding to that receptor via the inhibition of terminal glycosylation (Gasmi et al., 2021). Preceding to the SARS-CoV-2 pandemic, *in vitro* performance of CQ was investigated to hinder viral-replication. In these trails, the researchers came to found that cells pretreated with the 10μM concentration of CQ, inhibited the SARS-CoV replication as determined by immunofluorescence. In fact, earlier this March, Yao et al. reported antiviral-assay results using SARS-CoV-2-infected Vero cell lines they observed that HCQ was more effective than CQ against SARS-CoV-2. Liu et al. used a colocalization immunofluorescence technique to examine SARS-CoV-2 specific virion entrance into the endosome lysosome in 2020. They discovered that as compared to untreated virally infected cells, cells treated with CQ or HCQ had much more virions in early endosomes and relatively few in endolysosomes. Furthermore, these data revealed that both HCQ and CQ inhibited SARS-CoV-2 replication in vitro (Klouda and Stone, 2020).

Remdesivir

Nucleotide prodrug remdesivir (GS-5734) is absorbed into the developing RNA product and permits the addition of three more nucleotides before RNA synthesis halts. Remdesivir was manufactured and established by Gilead Sciences for the aid to treat *in vitro* against a broad array of many RNA-viruses from different families, including the Ebola, MERS-CoV, SARS-CoV, respiratory syncytial, Nipah, and Hendra virus (Ansems et al., 2021). Remdesivir also inhibits the RdRp of SARS-CoV-2. In addition, it has recently been acknowledged as a bright antiviral drug *in vivo* against SARS-CoV-2 replication in cell culture, non-human primate and mice models (Beigel et al., 2020). Human airway epithelial cells studies suggested that remdesivir helps in the inhibition of MERS-CoV and SARS-CoV. Whilst efficacy studies in mice reported that remdesivir obtained therapeutic-efficacy toward MERS-CoV in Ces1c−/− mice, lacking a secreted carboxylesterase liable for weak pharmacokinetics profiling of remdesivir in mice, when used earlier the peak of virus-replication (Ferner and Aronson, 2020).

Lopinavir/ritonavir

Lopinavir/ritonavir are drugs involved in inhibiting HIV proteases that converts Gag-Pol polyprotein precursors to fully mature protein, this inhibition results in formation of noninfectious and immature viral particle (Verdugo-Paiva et al., 2020). A study by (Verdugo-Paiva et al., 2020) where 199 COVID-19 patients were included, 99 were given ritonavir/lopinavir, while the remaining patients were exposed to standard care. At the end of the 28 days' treatment, no difference was observed in clinical improvements of the patients between both groups. Similar mortality was observed group treated with lopinavir-ritonavir group and the standard care. Hence, they did not notice any assistance with ritonavir/lopinavir dealing elsewhere standard care in the COVID-19 patients (Verdugo-Paiva et al., 2020). This could be explained by the fact that lopinavir/ritonavir were originally developed for inhibiting the HIV proteases (Ye et al., 2020).

It is an approved or evaluated drug for treating influenza and SARS-CoV-2 virus-infected patients in Japan, and China, respectively (Chen et al., 2020). It is a nucleoside precursor and the molecular mechanism includes the formation of a triphosphate form (T705-RTP) by intracellular phosphoribosylation (Cao et al., 2020). This triphosphate is accommodated by the viral RdRp [84], thus blocking viral replication and transcription (Cao et al., 2020). Several clinical-trials are being conducted to assess the safety and effectiveness of the favipiravir in different combinations in COVID-19 patients. According to preliminary results on 80 patients who were administered favipiravir was found that is more potent than lopinavir/ritonavir in terms of antiviral action in COVID-19 patients with no major adverse effects (Alhumaid et al., 2020).

Vaccinations against Covid-19 and their mode of actions

Currently a number of studies were directed towards the development of active immunization strategies. Whole virus vaccines, DNA and mRNA vaccines, synthetic peptide or epitope vaccines and subunit vaccines. Beside this the inactivated virions, recombinant antigen and adenoviral vectors are also investigated.

Table 1. Vaccination brands with corresponding manufacturing country

Vaccine brand	Type	Manufacturing country
Janssen vaccine or JNJ-78436725	Non-replicating viral vector	For "Emergency use" in U. K
Moderna or MRNA-1273	RNA-Based vaccine	In Canada, Israel, Switzerland, E.U, U.S, U. K
Pfizer-BioNTech or BNT162	RNA-Based vaccine	In Mexico, Argentina, Canada, US, UK, Saudi Arabia, Bahrain.
AstraZeneca/IQVIA	Non-Replicating viral vector	In Brazil, India, Pakistan, Morocco, U.K, El-Salvador
Anhui Zhifei longcom /Zifivax ZF2001	Protein Subunit	For "Emergency Use" in China & Uzbekistan
Gam-COVID-Vac	Nom- Replicating viral vector	In Algeria, Argentina, Bolivia, Hungary, UAE, Venezuela, Palestine, Paraguay.
Shenzhen kangtai vaccine	Inactivated virus	For "Emergency use "in China
Vaxine/ COVAX-19 vaccine	Protein Subunit	For "Emergency use" in Iran
QazCOVID-IN/ QazVac	Inactivated virus	Through "temporary registration" in Kazakhstan
Novavax /NVX-CoV2373	Protein Subunit	For "Emergency Use" in Indonesia & the Philippines.
BBIBP-CorV	Inactivated virus	For "Emergency use" in China & UAE.
Sinovac-CoronaVac	Inactivated virus	For "Emergency use" in China, Brazil, Indonesia

Whole virus vaccines

Inactive whole vaccines or live attenuated vaccines correspond a standard approach for viral vaccinations (Premikha et al., 2022). The inactivated SARS-CoV vaccine was the only one that has been tried for clinical trials in China (Hotez and Bottazzi, 2022). The successful sequencing and submission of first SARS-CoV-2 [(Wuhan-Hu1) to GenBank took place on January 05, 2020 with accession no. MN908947. Afterward, mass-scale culturing of SARS-CoV-2 was swiftly initiated. The establishment of an inactivated viral vaccine might be performed by mean of different chemical and physical methods such as formaldehyde, β-propiolactone and UV light (Ndwandwe and Wiysonge, 2021). The same way, at the University of Hong Kong, some researchers have established a live influenza-vaccine that expresses SARS-CoV-2 proteins. Additionally, Johnson & Johnson is a well-known multinational company boarding on COVID-19 vaccines; like their Ebola-vaccine route, they are engaging Janssen's adenoviral-vector AdVac® and engineering their PER-C6® cell-line technology. Lastly, Codagenix has established a "codon deoptimization" tools to manufacture viruses and is discovering SARS-CoV-2 vaccine tactics. Inactivated SARS-vaccines have been stated to prompt systemic-humoral-immunity in mice as well as high titters of S protein-specific antibodies that chunk binding to receptors and viral entrance to cell culture (Galili, 2021). Attenuated vaccine could also be helpful in a very potential way to elicit cross protection against heterologous strain that spread over within a beta CoV-lineage, such as bat SARS-like strains (Belete, 2020).

DNA and mRNA vaccine

The most advanced defence against the evolving illnesses was provided by the DNA vaccine. Additionally, the DNA vaccine was the first contender to reach clinical testing less than a year after the Zika virus outbreak (Silveira et al., 2021). SARS and MERS-CoV DNA vaccines usually perform better in DNA Prime/Heterologous boost regimens (inactivated virus, S/S1 proteins, or recombinant viral-vectors) (Seneff and Nigh, 2021). One potential benefit of mRNA vaccines is the induction of a strong and long-lasting immunological response (Park et al., 2021). It has been proven that for mRNA vaccines to function to their maximum capacity, an efficient and well-tolerated delivery route is required. mRNA

administered intramuscularly with first-generation lipid nanoparticles elicited a strong immune response, according to several pre-clinical and clinical research (Abbasi, 2020). It is presently uncertain if DNA vaccines given using electroporation have the potential for genomic integration and persistence. As an alternative to traditional vaccination methods, mRNA vaccines, on the other hand, provide a high level of effectiveness, quicker production cycles, lower manufacturing costs, and safe administration (Noor, 2021). There is still time to standardise its excellence and security assessment because no mRNA vaccine has yet to be released on the market. SARS-CoV-2 and Moderna's mRNA vaccine (mRNA-1273, which encodes S-protein) have so far been connected through animal testing and clinical batch production. INO-4800, a potential DNA vaccine candidate, is presently undergoing phase I clinical trials at Inovio-Pharmaceuticals. A partnership between Takis-Biotech, LineaRx, and Applied-DNA Sciences Subsidiary is currently in the pre-clinical stages with the aim of creating a SARS-CoV-2 linear DNA vaccine candidate (Pang et al., 2022).

Epitope/synthetic peptide vaccination

Chemical processes are widely used to create synthetic vaccinations, which are made up of a few fragments of whole antigens (Houghton et al., 1999). Their low molecular weight and structural complexity, despite their fundamental structure and quality control, may lead to decreased immunogenicity. As a result, during formulation, morphological modifications, delivery systems, and adjuvants are also required (Köseoğlu et al., 2022). A group of B-cell and T-cell epitopes from the N and S proteins of the SARS-CoV are being monitored by scientists at Hong Kong University of Science and Technology. These epitopes are remarkably preserved in the virus and may help experimental efforts to create SARS-CoV-2 vaccines (RAIH et al., 2022).

The subunit vaccines

Subunit vaccines like the S-protein and/or the RBD component of SARS-CoV-2 must be specifically targeted by vaccination (Heidary et al., 2022). The B- and T-cell response will be boosted, and viral infection will be avoided. Nearly every Institute engaged in the development of a SARS-CoV-2 subunit vaccine uses and/or has ingested the S protein as an antigen. For instance, research on a subunit vaccination based on "molecular clamp" technology is being done at the University of Queensland. Using "Trimer-Tag" methods, Clover-Biopharmaceuticals Inc. is also creating a vaccine candidate against SARS-CoV-2 (Ortega-Rivera et al., 2021).

Convalescent plasma therapy (CP)

The convalescent plasma therapy intent to extract and use the antibodies from the blood of recovered patients from COVID-19 for the sake to treat the critically affected patients by SARS-CoV-2 (Focosi et al., 2020). This therapy could also be used to immunize those at a high risk of attracting the virus such as doctors, nurses, patient's families and other high-risk contacts.

This concept suggests that once the recovered individual antibodies transferred to other patients under treatment, will start fighting and targeting the 2019-nCoV in the secondary patients. A few studies presented a shorten hospital stay and minimum-mortality rate in patients cured with CP than those, who were not cured with CP (Rojas et al., 2020). In fact, in 2014, the use of CP was done by WHO as an empirical treatment during pandemic when some patients were recovered from Ebola virus. In addition, recently this therapy has been used for the treatment of MERS-CoV, showing efficient inactivation of this virus (Wood et al., 2021).

A perspective cohort study was reported by Hung et al. clarified a significant lessening of mortality in patients cured with CP during influenza pandemic 2009 (H1N1) virus infection. A meta-analysis by Luke et al. that included 1703 patients with influenza-pneumonia from 1918-1925, who took a portion of influenza-convalescent human blood-products showed an association with a decrease in mortality among patients who received treatment (Wood et al., 2021). Another meta-analysis showed the mortality was bated afterward administering different quantities of CP in patients with SARS infection, with lower side or adverse impacts after treatment.

The CP therapy is similar to passive immunization as, many researchers suggested, it is a preventive measure rather that a treatment for COVID-19 (Duan et al., 2020).

Pfizer-BioNTech COVID-19 vaccine

During the mid of December 2020, the U.S. Food and Drug Administration (FDA) issued the first emergency use authorization for a vaccine against COVID-19 caused by SARS-CoV-2 named BNT162b2, which is also known under the name Comirnaty. For the first time after COVID-19 infection, distribution rights were granted to Pfizer-BioNTech. The effectiveness of this vaccination against COVID-19 is 95.3%. The S glycoprotein of SARS-CoV-2 is encoded by nucleoside-modified messenger RNA (modRNA), which is part of the Pfizer-BioNTech COVID-19 vaccine. The SARS-CoV-2 S antigen can be created in host cells thanks to the lipid particles used in the creation of the modRNA vaccination. As a result, this vaccination's S antigen triggers an immune response that protects against COVID-19 (Oliver et al., 2020).

The common side effects during treatment which normally prevailed 1-3 days, includes pain after injection (92%), headache (64.7%), exhausted body (70%), pain in muscles and joints, chills (45.4%), fever (15.5%), myalgia (61.5%) etc. and reveal that an immune system is provoked (Shimabukuro, 2021). Vaccination with Pfizer BioNTech was linked with an increased risk of myocarditis. Mostly people complained these side effects after the 2nd dose vaccine treatment. So, companies need to consider these side effects may arise not only during 1st but 2nd dose too. There are estimates regarding vaccine production given by Pfizer that 50 million doses are expected to be produced during 2020. However, this level may rise up to 1.3 billion at the end 2021 (Lebedev et al., 2021). The health care medical specialists are on top priority to get vaccinations than institutional staffs of care homes, higher risk persons, senior citizens aged greater than 65, furthermore distributed to common patients (Tano et al., 2021).

Recent developments of immunization against COVID-19

The development of vaccines for the five epidemic pathogens on the WHO's priority list is supported by a small number of organisations, including the Coalition for Epidemic Preparedness-Innovation (CEPI), an international non-governmental organisation supported by the Welcome Trust, the Bill and Melinda Gates Foundation, the European Commission, and eight countries (Belgium, Australia, Canada, Germany, Ethiopia, Norway, Japan, and the United Kingdom) (Andreadakis et al., 2020). A successful method would be able to generate predictable immune responses via pathogens, maintain growth from viral sequencing through clinical trials lasting less than 16 weeks, and be suitable for thorough engineering on a pathogen-agnostic platform. The COVID-19 vaccine-R&D landscape will consist of 115 vaccines on or after April 8, 2020, of which 78 have been verified to be active and the remaining 37 have not (progress position cannot be strong-minded from overtly obtainable or exclusive info sources). Currently, research or pre-clinical stages are being pursued by 73 of the 78 verified ongoing activities (Yan et al., 2021). The most advanced rivals have just recently begun clinical trials, including Moderna's mRNA-1273, CanSino-Biologicals' Ad5-nCoV, Inovio's INO4800, LV-SMENP-DC, and Shenzhen Geno-Immune Medical Institute's pathogen-specific aAPC (Ndwandwe and Wiysonge, 2021).

DISCUSSION

CQ was first time manufactured in 1934 and had been ordained broadly for the prevention and cure aid of malaria and autoimmune disease such as system lupus erythematosus and rheumatoid arthritis (Touret and de Lamballerie, 2020). Additionally, both agents have also shown an effective therapeutic and immune-modulatory effect against broad range of other diseases such as HIV, amebiasis, antiphospholipid syndrome and cancer (Cortegiani et al., 2020). The active mechanism of both CQ and HCQ against SARS-CoV-2 is yet to be entirely clarified. CQ was initially underlined during 2002-2003 SARS-CoV epidemic (Meo et al., 2020). Research on the original SARS-CoV has shown that SARS-CoV-2 enters cells by

binding to a receptor called ACE2, and CQ may inhibit terminal glycosylation to prevent the virus from binding to ACE2. Prior to the SARS-CoV-2 pandemic, researchers looked at CQ's ability to prevent viral replication in vitro. As determined by immunofluorescence in these tests, the researchers found that pretreatment of cells with 10 M CQ inhibited SARS-CoV replication (Moore, 2020). Earlier this month, Yao et al. presented antiviral-assay results using Vero cell lines infected with SARS-CoV-2. They noted that HCQ was superior than CQ in its ability to combat SARS-CoV-2 (Ferner and Aronson, 2020). In 2020, Liu et al. investigated the entry of the SARS-CoV-2 specific virion into the endosome lysosome using a colocalization immunofluorescence method. They found that cells treated with CQ or HCQ had much more virions in early endosomes and very few in endolysosomes compared to virally infected cells that had not been treated. Furthermore, these results showed that SARS-CoV-2 replication in vitro was inhibited by both HCQ and CQ (Devaux et al., 2020).

The ethnobotanical medicine and phytochemicals against COVID-19 has been explored by many researchers. Some of the most potent medicinal plants for COVID-19 treatments are, *Nigella sativa*, *Eurycoma longifolia*, *Vernonia amygdalina*, *Azadirachta indica* with potent immunomodulatory, anti-inflammatory and antiviral properties (Lim et al., 2021).

https://www.frontiersin.org/articles/10.3389/fphar.2021.611408/full

ACKNOWLEDGEMENTS

This work is dedicated to the doctors, nurses, laboratory technicians and health personnel who fight against this pandemic, as well as our COVID-19 patients, and their families.

CONFLICT OF INTEREST STATEMENT

The authors declare that this research was conducted in the absence of any potential conflict of interest.

REFERENCES CITED

Abbasi, J. 2020. COVID-19 and mRNA vaccines—first large test for a new approach. Jama. 324(12):1125-1127

Alhumaid, S., A. Al Mutair, Z. Al Alawi, N. Alhmeed, A.R.Z. Zaidi and M. Tobaiqy. 2020. Efficacy and safety of lopinavir/ritonavir for treatment of COVID-19: a systematic review and meta-analysis. Tropical medicine and infectious disease. 5(4):180

Andreadakis, Z., A. Kumar, R.G. Román, S. Tollefsen, M. Saville and S. Mayhew. 2020. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 19(5):305-306

Ansems, K., F. Grundeis, K. Dahms, A. Mikolajewska, V. Thieme, V. Piechotta, M.-I. Metzendorf, M. Stegemann, C. Benstoem and F. Fichtner. 2021. Remdesivir for the treatment of COVID-19. Cochrane Database of Systematic Reviews.(8)

Beigel, J.H., K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer and S. Kline. 2020. Remdesivir for the treatment of Covid-19. New England Journal of Medicine. 383(19):1813-1826

Belete, T.M. 2020. A review on Promising vaccine development progress for COVID-19 disease. Vacunas. 21(2):121-128

Cao, B., Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai and M. Wei. 2020. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine.

Chan, J.F., S.K. Lau, K.K. To, V.C. Cheng, P.C. Woo and K.-Y. Yuen. 2015. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clinical microbiology reviews. 28(2):465-522

Chen, C., J. Huang, Z. Cheng, J. Wu, S. Chen, Y. Zhang, B. Chen, M. Lu, Y. Luo and J. Zhang. 2020

Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv.

Cortegiani, A., G. Ingoglia, M. Ippolito, A. Giarratano and S. Einav. 2020. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. Journal of critical care. 57:279-283

Devaux, C.A., J.-M. Rolain, P. Colson and D. Raoult. 2020. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? International journal of antimicrobial agents. 55(5):105938

Dhama, K., S.K. Patel, K. Sharun, M. Pathak, R. Tiwari, M.I. Yatoo, Y.S. Malik, R. Sah, A.A. Rabaan

and P.K. Panwar. 2020. SARS-CoV-2 jumping the species barrier: zoonotic lessons from SARS, MERS and recent advances to combat this pandemic virus. Travel medicine and infectious disease. 37:101830

Duan, K., B. Liu, C. Li, H. Zhang, T. Yu, J. Qu, M. Zhou, L. Chen, S. Meng and Y. Hu. 2020. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences. 117(17):9490-9496

Erickson, T., P. Chai and E. Boyer. 2020. Chloroquine, hydroxychloroquine and COVID-19. Toxicology communications. 4(1):40-42

Ferner, R.E. and J.K. Aronson. 2020. Chloroquine and hydroxychloroquine in covid-19, British Medical Journal Publishing Group. 369.

Ferner, R.E. and J.K. Aronson. 2020. Remdesivir in covid-19, British Medical Journal Publishing Group. 369.

Focosi, D., A.O. Anderson, J.W. Tang and M. Tuccori. 2020. Convalescent plasma therapy for COVID-19: state of the art. Clinical microbiology reviews. 33(4):e00072-00020Frutos, R., J. Serra-Cobo, L. Pinault, M. Lopez Roig and C.A. Devaux. 2021. Emergence of bat-related betacoronaviruses: hazard and risks. Frontiers in microbiology. 12:591535

Galili, U. 2021. COVID-19 variants as moving targets and how to stop them by glycoengineered whole-virus vaccines. Virulence. 12(1):1717-1720

Gasmi, A., M. Peana, S. Noor, R. Lysiuk, A. Menzel, A. Gasmi Benahmed and G. Bjørklund. 2021. Chloroquine and hydroxychloroquine in the treatment of COVID-19: the never-ending story. Applied microbiology and biotechnology. 105(4):1333-1343

Ge, X.Y., B. Hu and Z.L. Shi. 2015. Bat coronaviruses. Bats and Viruses: A new frontier of emerging infectious diseases.127-155

Graham, R.L., E.F. Donaldson and R.S. Baric. 2013. A decade after SARS: strategies for controlling emerging coronaviruses. Nature Reviews Microbiology. 11(12):836-848

Heidary, M., V.H. Kaviar, M. Shirani, R. Ghanavati, M. Motahar, M. Sholeh, H. Ghahramanpour and S. Khoshnood. 2022. A comprehensive review of the protein subunit vaccines against COVID-19. Frontiers in microbiology. 13:927306

Hotez, P.J. and M.E. Bottazzi. 2022. Whole inactivated virus and protein-based COVID-19 vaccines. Annual Review of Medicine. 73:55-64

Houghton, R.L., D.R. Benson, L.D. Reynolds, P.D. McNeill, P.R. Sleath, M.J. Lodes, Y.A. Skeiky, D.A. Leiby, R. Badaro and S.G. Reed. 1999. A multi-epitope synthetic peptide and recombinant protein for the detection of antibodies to Trypanosoma cruzi in radioimmunoprecipitation-confirmed and consensus-positive sera. The Journal of infectious diseases. 179(5):1226-1234

Hu, B., X. Ge, L.-F. Wang and Z. Shi. 2015. Bat origin of human coronaviruses. Virology journal. 12(1):1-10

Khan, M., S.F. Adil, H.Z. Alkhathlan, M.N. Tahir, S. Saif, M. Khan and S.T. Khan. 2020. COVID-19: a global challenge with old history, epidemiology and progress so far. Molecules. 26(1):39

Klouda, C.B. and W.L. Stone. 2020. Oxidative stress, proton fluxes, and chloroquine/hydroxychloroquine treatment for COVID-19. Antioxidants. 9(9):894

Köseoğlu, A.E., H. Can, M. Güvendi, S.E. Alak, A.D. Döşkaya, M. Karakavuk, M. Döşkaya and C. Ün. 2022. Molecular characterization of Anaplasma ovis Msp4 protein in strains isolated from ticks in Turkey: A multi-epitope synthetic vaccine antigen design against Anaplasma ovis using immunoinformatic tools.

Latif, A.A. and S. Mukaratirwa. 2020. Zoonotic origins and animal hosts of coronaviruses causing human disease pandemics: A review. Onderstepoort Journal of Veterinary Research. 87(1):1-9

Lebedev, L., M. Sapojnikov, A. Wechsler, R. Varadi-Levi, D. Zamir, A. Tobar, N. Levin-Iaina, S. Fytlovich and Y. Yagil. 2021. Minimal change disease following the Pfizer-BioNTech COVID-19 vaccine. American Journal of Kidney Diseases. 78(1):142-145

Lei, Z.-N., Z.-X. Wu, S. Dong, D.-H. Yang, L. Zhang, Z. Ke, C. Zou and Z.-S. Chen. 2020. Chloroquine and hydroxychloroquine in the treatment of malaria and repurposing in treating COVID-19. Pharmacology & Therapeutics. 216:107672

Mackay, I.M. and K.E. Arden. 2015. Middle East respiratory syndrome: an emerging coronavirus infection tracked by the crowd. Virus research. 202:60-88

Meo, S., D. Klonoff and J. Akram. 2020. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. Eur Rev Med Pharmacol Sci.4539-4547

Moore, N. 2020. Chloroquine for COVID-19 infection, Springer. 43**:** 393-394.

Ndwandwe, D. and C.S. Wiysonge. 2021. COVID-19 vaccines. Current opinion in immunology. 71:111-116

Noor, R. 2021. Developmental Status of the Potential Vaccines for the Mitigation of the COVID-19 Pandemic and a Focus on the Effectiveness of the Pfizer-BioNTech and Moderna mRNA Vaccines. Current clinical microbiology reports. 8(3):178-185

Oliver, S.E., J.W. Gargano, M. Marin, M. Wallace, K.G. Curran, M. Chamberland, N. McClung, D. Campos-Outcalt, R.L. Morgan and S. Mbaeyi. 2020. The advisory committee on immunization practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine-United States, December 2020. Morbidity and mortality weekly report. 69(50):1922

Ortega-Rivera, O.A., M.D. Shin, A. Chen, V. Beiss, M.A. Moreno-Gonzalez, M.A. Lopez-Ramirez, M. Reynoso, H. Wang, B.L. Hurst and J. Wang. 2021. Trivalent subunit vaccine candidates for COVID-19 and their delivery devices. Journal of the American

Chemical Society. 143(36):14748-14765

Pang, A.P., A.T. Higgins-Chen, F. Comite, I. Raica, C. Arboleda, H. Went, T. Mendez, M. Schotsaert, V. Dwaraka and R. Smith. 2022. Longitudinal study of DNA methylation and epigenetic clocks prior to and following test-confirmed COVID-19 and mRNA vaccination. Frontiers in Genetics. 13:819749

Parihar, S., R.J. Kaur and S. Singh. 2021. Flashback and lessons learnt from history of pandemics before COVID-19. Journal of Family Medicine and Primary Care. 10(7):2441

Park, J.W., P.N. Lagniton, Y. Liu and R.-H. Xu. 2021. mRNA vaccines for COVID-19: what, why and how. International journal of biological sciences. 17(6):1446

Pereira, B.B. 2020. Challenges and cares to promote rational use of chloroquine and hydroxychloroquine in the management of coronavirus disease 2019 (COVID-19) pandemic: a timely review. Journal of Toxicology and Environmental Health, Part B. 23(4):177-181

Poudel, U., D. Subedi, S. Pantha and S. Dhakal. 2020. Animal coronaviruses and coronavirus disease 2019: Lesson for one health approach. Open veterinary journal. 10(3):239–251-239–251

Premikha, M., C.J. Chiew, W.E. Wei, Y.S. Leo, B. Ong, D.C. Lye, V.J. Lee and K.B. Tan. 2022. Comparative Effectiveness of mRNA and Inactivated Whole-Virus Vaccines Against Coronavirus Disease 2019 Infection and Severe Disease in Singapore. Clinical Infectious Diseases. 75(8):1442-1445

RAIH, F., N. ABDULLAH and S. SHAMSUDDIN. 2022. Construction of Multi-Epitopes Vaccine Candidate against SARS-CoV-2 D614G Variant. Sains Malaysiana. 51(9):2985-2997

Reperant, L.A. and A.D. Osterhaus. 2017. AIDS, Avian flu, SARS, MERS, Ebola, Zika… what next? Vaccine. 35(35):4470-4474

Rojas, M., Y. Rodríguez, D.M. Monsalve, Y. Acosta-Ampudia, B. Camacho, J.E. Gallo, A. Rojas-Villarraga, C. Ramírez-Santana, J.C. Díaz-Coronado and R. Manrique. 2020. Convalescent plasma in Covid-19: Possible mechanisms of action. Autoimmunity reviews. 19(7):102554

Seneff, S. and G. Nigh. 2021. Worse than the disease? Reviewing some possible unintended consequences of the mRNA vaccines against COVID-19. International Journal of Vaccine Theory, Practice, and Research. 2(1):38-79

Shimabukuro, T. 2021. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine—United States, December 14–23, 2020. American Journal of Transplantation. 21(3):1332

Silveira, M.M., G.M.S.G. Moreira and M. Mendonça. 2021. DNA vaccines against COVID-19: Perspectives and challenges. Life sciences. 267:118919

Tano, E., S. San Martin, S. Girgis, Y. Martinez-Fernandez and C. Sanchez Vegas. 2021. Perimyocarditis in adolescents after Pfizer-BioNTech COVID-19 vaccine. Journal of the Pediatric Infectious Diseases Society. 10(10):962-966

Touret, F. and X. de Lamballerie. 2020. Of chloroquine and COVID-19. Antiviral research. 177:104762

Tripathy, S., B. Dassarma, S. Roy, H. Chabalala and M.G. Matsabisa. 2020. A review on possible modes of action of chloroquine/hydroxychloroquine: repurposing against SAR-CoV-2 (COVID-19) pandemic. International journal of antimicrobial agents. 56(2):106028

Tsang, W. 2014. Viral Myths and Biopolitical Disruptions amidst the Emergence of a Novel Coronavirus.

Verdugo-Paiva, F., A. Izcovich, M. Ragusa and G. Rada. 2020. Lopinavir-ritonavir for COVID-19: A living systematic review. Medwave.e7967-e7967

Wood, E.M., L.J. Estcourt and Z.K. McQuilten. 2021. How should we use convalescent plasma therapies
for the management of COVID-19? Blood. 137(12):1573-1581

Yan, Y., Y. Pang, Z. Lyu, R. Wang, X. Wu, C. You, H. Zhao, S. Manickam, E. Lester and T. Wu. 2021. The COVID-19 vaccines: recent development,

challenges and prospects. Vaccines. 9(4):349

Ye, X., Y. Luo, S. Xia, Q. Sun, J. Ding, Y. Zhou, W. Chen, X. Wang, W. Zhang and W. Du. 2020. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. Eur Rev Med Pharmacol Sci.3390-3396

Zhou, Z., Y. Qiu and X. Ge. 2021. The taxonomy, host range and pathogenicity of coronaviruses and other viruses in the Nidovirales order. Animal Diseases. 1(1):1-28.

Lim, X. Y., Teh, B. P., & Tan, T. Y. C. 2021. Medicinal plants in COVID-19: potential and limitations. Frontiers in pharmacology, 12, 611408.

Greenwood B.M., Bojang K., Whitty C.J., Targett G.A. Malaria. Lancet. 2005; 365:1487–1498.

Inklebarger, J. J. I. J., Gyer, M., Galanis, N., Michael, M., & Adel, D. 2020. Cinchona bark for the treatment of Covid-19 Pnemonia: A modern review of the potential anti-viral therapeutic applications of an old treatment. International Journal of Medical Science and Clinical Invention, 7(05), 4795-4801.