Journal of Contemporary Issues in Business and Government Vol. 26, No. 2, 2020
https://cibg.org.au/

P-ISSN: 2204-1990; E-ISSN: 1323-6903
DOI: 10.47750/cibg.2020.26.02.179

Hydroxychloroquine- A Saviour from The Past - A Review

KARISHMA DESAI[1], LAKSHMINARAYANAN ARIVARASU[2*], LESLIE RANI. S[3]

[1]Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
[2]Assistant professor, Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
[3]Department of General Pathology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
*Corresponding Author
Email**:** 151801002.sdc@saveetha.com[1], lakshmin.sdc@saveetha.com[2], leslieranis.sdc@saveetha.com[3]

Abstract: Hydroxychloroquine is a widely used anti-malarial drug that has been under study for its effect against coronavirus. It has a wide range of applications for various reasons. It also causes certain side effects in the human body when consumed for long. HCQ has been a proven treatment plant for autoimmune disorders like rheumatoid arthritis and SLE. Hydroxychloroquine is a widely used anti-malarial drug. It possesses various benefits and is also used in autoimmune disorders like lupus and rheumatoid arthritis. Hydroxychloroquine sulfate is known to be a derivative of Chloroquine. In this review, we aim to analyze the properties of HCQ, know about the side effects and understand its role in treating COVID-19 and summarize our observations. A systematic search strategy was employed and articles were found using keywords. Literature was taken from databases like PubMed and Google Scholar. Articles that discussed the use of HCQ in COVID-19 were included. Other articles which had data regarding HCQ- side effects, structure and its applications were also included. A total of about 70 articles were collected initially. Multiple articles were added later from other sources. After eliminating articles that did not meet the inclusion criteria, more than 30 studies were finally obtained. This review summarized the use of HCQ in COVID-19. Its structure, and other roles in treatment of Autoimmune disorders were also discussed in detail.

Keywords: Hydroxychloroquine; COVID-19; Chloroquine; Drugs used in COVID-19; Anti-malarial; Autoimmune disorders

INTRODUCTION

Coronavirus Disease 2019- also known as COVID-19 is a severe acute respiratory disease. It originated in Wuhan province in China. Because of the mode of transmission, it spread very rapidly and soon became a worldwide pandemic. Because of the speed at which it is spreading and its symptoms, it makes it way more dangerous and has consumed lots of lives of people worldwide. There has been no proven cure to the disease. No drugs have been proven to work on this virus and kill it effectively in humans. The only methods that can be employed are maintaining social distancing, sanitizing regularly, wearing a mask, and not ignoring symptoms of this deadly disease. There are multiple symptoms to look out for; breathlessness/ breathing difficulty is the major symptom. It is necessary to look out for these symptoms in children as well. Neglect can lead to serious complications. (Gurunathan and Shanmugaavel, 2016)Obstructive airway illnesses are manifested with chronic inflammation affecting the whole respiratory tract.(Dave and Preetha, 2016) Recently, even loss of ability to detect taste and smell is also a sign to be taken seriously. The other symptoms include fever, chills, excess cough, etc. The testing for this disease is being done widely. The only solution as of now is isolation of the patient that has tested positive. Scientists have been looking out for multiple drugs that may have an effect on the virus. Chloroquine and its hydroxy analogue, Hydroxychloroquine are being suggested as treatment options for COVID-19. It was recommended by the Chinese Officials to facilitate use of these drugs as a potential cure to this viral disease. In recent years, resistance to drugs has increased greatly. This makes it difficult to find an ideal drug to cure. (Selvan and Ganapathy, 2016)

Hydroxychloroquine sulfate is known to be a derivative of Chloroquine; it was first synthesized in the year 1946, by the introduction of a hydroxyl group into the structure of the normal Chloroquine. Hydroxychloroquine is a very widely used anti-malarial drug. It is popularly known by its brand name called Plaquenil. It has shown a good activity against a variety of viruses in vitro. (Owens, 2020) It is known to be a very pocket friendly drug and is mostly safe. (Singh *et al.*, 2020) The role of hydroxychloroquine is effective in treatment of Auto-

immune diseases like rheumatoid arthritis. (Liu *et al.*, 2020) Hydroxychloroquine has been demonstrated to have an anti- SARS- and CoV activity which is proven in vitro. This drug has been under study for more than 40 years now, but still is not used as an antiviral. It is being studied for a very long period of time but there is no effect that is known against the virus. (Lover, no date) There is no clear mode of action for this drug, but it is known to reduce the acidity in the endosomes. This reduction in acidity might prevent the endosomes from releasing the virus into the cytoplasm. If this occurs then the spread of the virus can be stopped. Another MOA is that this drug inhibits receptor binding membrane fusion which is required for the entry of coronavirus. (Zhou, Dai and Tong, 2020)

Since Hydroxychloroquine has already been studied thoroughly, we know that it is a proven medication for the treatment of autoimmune diseases such as Lupus and Rheumatoid Arthritis.These autoimmune diseases have to be treated or may proceed to further complications like hepatic fibrosis. (Ezhilarasan, Sokal and Najimi, 2018) After the time of the COVID-19 outbreak, it was suggested by Chinese Health Officials that Hydroxychloroquine may be useful. This suggestion brought about more research being carried out on this drug, its activity on the virus and its side effects caused if any. Many researches have already been done extensively regarding these drugs. Hydroxychloroquine is used in certain cases of diabetes mellitus as well.(Wondafrash *et al.*, 2020) It can bring about toxic effects when it is given in higher doses without proper administration.(Jordan *et al.*, 1999) Lately, the use of Hydroxychloroquine in the treatment of COVID-19 is under study. There is no proven effect of this drug against the virus as of now (Yazdany and Kim, 2020)**.** This drug is also used in lupus pregnancy (Clowse *et al.*, 2006). Some articles also show that hydroxychloroquine may cause ocular toxicity as a major side effect. (Tehrani *et al.*, 2008) The pharmacological properties as well as therapeutic effects of HCQ have been reviewed in many studies. (Rainsford *et al.*, 2015) This review will prove useful because Hydroxychloroquine can be a possible cure to COVID-19. It is necessary to analyze this drug in detail and learn about its effectiveness. This drug is also a known medication for treating rheumatoid arthritis. It is useful in successfully reducing stiffness in cases of arthritis. It is also used by patients having systemic lupus erythematosus. Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Deogade, Gupta and Ariga, 2018; Ezhilarasan, 2018; Ezhilarasan, Sokal and Najimi, 2018; Jeevanandan and Govindaraju, 2018; J *et al.*, 2018; Menon *et al.*, 2018; Prabakar *et al.*, 2018; Rajeshkumar, Kumar, *et al.*, 2018; Vishnu Prasad *et al.*, 2018; Wahab *et al.*, 2018; Dua *et al.*, 2019; Duraisamy *et al.*, 2019; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Gheena and Ezhilarasan, 2019a; Malli Sureshbabu *et al.*, 2019; Mehta *et al.*, 2019; Panchal, Jeevanandan and Subramanian, 2019; Rajendran *et al.*, 2019; Rajeshkumar *et al.*, 2019; Ramakrishnan, Dhanalakshmi and Subramanian, 2019; Sharma *et al.*, 2019; Varghese, Ramesh and Veeraiyan, 2019; Gomathi *et al.*, 2020; Samuel, Acharya and Rao, 2020)

The most important function of HCQ is that it is an anti-malarial drug. The aim of this review is to learn more about HCQ, its benefits, its drawbacks and most importantly, its role in COVID-19.

COVID-19

Coronaviruses are a group of RNA viruses that are broadly distributed among the human population. They are known to cause diseases in humans(Chen, Liu and Guo, 2020). Coronavirus primarily attacks the respiratory system of humans. The disease is transmitted by droplets of an infected person to a health person. The symptoms of this disease may start appearing in approximately 5 days, but it may take longer to show symptoms or some people that are affected might even be asymptomatic(Rothan and Byrareddy, 2020). The spread of this deadly disease started from Wuhan in China. It rapidly spread to other parts of China and then to different countries and soon spread throughout the world. It was declared as a pandemic in no time (Lipsitch, Swerdlow and Finelli, 2020). There are a wide range of symptoms that can be observed in patients affected with this virus. Breathlessness is the first sign to look out for in such cases. Other symptoms that follow are sore throat, cough, loss of ability to taste and smell, etc (Sohrabi *et al.*, 2020). At first, this disease was identified as pneumonia but its cause was unknown and not diagnosed accurately (Guan *et al.*, 2020). These groups of coronaviruses are very dangerous to the human body. They can infect the hepatic system as well as the nervous system in humans. Their main mode of action is attacking the respiratory system. As discussed earlier, the mode of spread of this viral infection is person-to-person transmission. This transmission can be from a carrier to an individual or from an infected person to another or even from a doctor to another patient (Bai *et al.*, 2020). A healthy person is one that is in a complete state of physical, mental and social well being(Subashri and Uma Maheshwari, 2016).

Treatment modalities

A variety of drugs have been under study to check for their activity against coronavirus. Multiple drugs from different backgrounds are being studied and researched extensively. They have various diverse active components which are responsible for their properties. (Perumalsamy *et al.*, 2018) In recent years, medicinal plants are being studied to find a substitute to conventional drugs. (Anitha and Ashwini, 2017) Most of these plants have a variety of biological properties that are of great use. (Ashwini, Ezhilarasan and Anitha, 2017) (Ezhilarasan, Lakshmi, Vijayaragavan, *et al.*, 2017) Some of these properties include Anti-inflammatory, Anti-

malarial, Anti-bacterial, Cytotoxic effects etc. (Lakshmi *et al.*, 2015) (Ezhilarasan, Lakshmi, Nagaich, *et al.*, 2017) These plants provide good effects and show beneficial results according to their properties.(Ezhilarasan, 2018) Teicoplanin is a glycopeptide antibiotic that was used in the treatment of bacterial infections. It was found in a study that this drug is active against SARS CoV. This fact was proven in vitro (Baron *et al.*, 2020). Recently, Nanoparticles have gained widespread importance due to their antibacterial, antiviral, anti-inflammatory properties. Various nanoparticles are used widely in treatment protocols. Selenium, Silver, Zinc nanoparticles are some of the examples (Menon *et al.*, 2018)(Rajeshkumar, Kumar, *et al.*, 2018)(Karthiga, Rajeshkumar and Annadurai, 2018) (Rajeshkumar, Agarwal, *et al.*, 2018). These nanoparticles may find a role to play in treatment of this deadly disease.Even nano-carrier drug delivery systems have gained importance and are being used widely (Sharma *et al.*, 2019). Another addition to the list of possible treatment options was antiviral therapy. Antiviral therapy consists of giving a treatment of interferon alpha. This may decrease the viral load in the initial stages of the disease (Shen *et al.*, 2020). Litonavir/Lopinavir have also been tried and tested but as of now, their efficiency against the virus and safety of use has not been determined (*Website*, no date). In China, traditional Chinese medicines proved important in the treatment process. It brought about a new hope amongst the population to control the spread of this disease (Dong, Hu and Gao, 2020). Various drugs like Chloroquine, Arbidol, Remedesvir, Favipiravir are under different clinical studies. These studies are being carried out to check their efficacy against the virus (Xu *et al.*, 2020). Certain data showed that the drug Tocilizumab improved the clinical outcome in patients that were severely affected by the virus (Sallard *et al.*, 2020). It is suggested that interferon treatment can be performed in the early stages of viral infection (Baden and Rubin, 2020).Lopinavir and Ritonavir are popularly used antiviral drugs. They are known to have an activity against the enzyme protease. These drugs are also in the stage of clinical trials.(Cunningham, Goh and Koh, 2020) Oligonucleotides have been used previously for treatment of respiratory diseases such as COPD or Asthma. Their role in treatment of COVID-19 is not known as of now (Mehta *et al.*, 2019). Syringic acid has also been under study for its anti-inflammatory and antioxidant activity.It is used as a treatment for certain diseases(Gheena and Ezhilarasan, 2019b). Upcoming research shows that vitamin C is a very effective drug that can help with pain management. It can be an immunity booster in such conditions as well(Chaitanya *et al.*, 2018). In this study, the use of Hydroxychloroquine in curing this viral infection has been discussed in detail. At present, no specific regime, specific medication or specific vaccine has been found as a definitive solution to this virus(Ben-Zvi *et al.*, 2012).

Foreword to Hydroxychloroquine

Hydroxychloroquine is a widely used anti-malarial drug. It possesses various benefits and is also used in autoimmune disorders like lupus and rheumatoid arthritis. Even aloe vera has been proven to be useful in treating skin related problems in diseases(Selvan and Ganapathy, 2016; Subasree, Murthykumar and Dhanraj, 2016). It has great antibacterial and antiviral properties. In cases like cellulitis and others, oral antimicrobials are also given orally as a treatment(Vijayalakshmi and Ganapathy, 2016). These are attributed to its ability of alkalinisation. The pH is decreased in the intracellular acidic organelles and this prevents entry of bacteria and virus(Sahraei *et al.*, 2020). It is an orally administered drug, which is the predominant route of drug dosage(G *et al.*, 2017). Its mode of action is through inhibiting the binding to the receptor. This receptor binding is essential for the entry of coronavirus.

Structure of Hydroxychloroquine

The structure of Hydroxychloroquine and Chloroquine are not very different from each other, the difference is just an extra hydroxyl group. In hydroxychloroquine, N- Hydroxyethyl side chain is added and this makes Hydroxychloroquine more soluble than Chloroquine(Fox, 1993).

Overview of Applications

Hydroxychloroquine has a wide array of applications as an antimicrobial, antiplatelet antineoplastic and anti-thrombolytic agent. Anti- platelet drugs are employed to prevent arterial or venous thrombi. It is mainly used as an anti-malarial drug. The other applications of this drug are seen in autoimmune diseases like lupus and rheumatoid arthritis (Stein, Bell and Ang, 2000).

Potential Harmful Effects

As every drug has certain side effects, even Hydroxychloroquine has multiple harmful effects. It is necessary to analyse these effects and understand when to prescribe the drug and what reactions to expect. Hydroxychloroquine is proven to cause Ocular toxicity, Neuro-myotoxicity and retinopathy as well. These effects are dangerous side effects of consuming these drugs for a long period of time. Research is in progress to help overcome these drawbacks.(Touret and de Lamballerie, 2020)(Weiner *et al.*, 1991)

Added Benefits

Focussing on the benefits provided by this drug, we already know that it is a good antimalarial and anti-rheumatic drug. In cases of Lupus, which is an autoimmune disease, the symptoms are skin rashes and other skin related conditions. Hydroxychloroquine is a relatively safe drug to administer in such patients with skin conditions related to SLE. It is an extensively used drug. Recently, it has been found that this drug is also highly effective against the coronavirus and this fact has been proven in vitro (Molina *et al.*, 2020).

Role of hydroxychloroquine in COVID-19

After Hydroxychloroquine was suggested to be a treatment for COVID-19, it was used worldwide. But certain studies show that it has no strong effect on the patients that are suffering from COVID-19(Rathi *et al.*, 2020).Hydroxychloroquine has been used as a prophylaxis for frontline healthcare workers who are treating the patients that are suffering from this disease(Ferner and Aronson, 2020). As the toxic effects of using Hydroxychloroquine have already been discussed, it is known that the use of Hydroxychloroquine is not guaranteed to be completely safe. In some cases, it may cause adverse cutaneous reactions as a toxic effect. Because of the widespread consumption of Hydroxychloroquine and Chloroquine around the world, it even brought about a shortage of drugs for people that used it for auto-immune diseases like SLE in which Hydroxychloroquine was already proven as an effective treatment choice [(Rome and Avorn, 2020)Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

CONCLUSION

The aim of this review was to have an overall knowledge about Hydroxychloroquine. This included a detailed discussion about the side effects, applications and structure of Hydroxychloroquine. The role of HCQ in treatment of COVID-19 is still not clearly stated. There needs to be more extensive research that should be conducted to help understand how HCQ can be helpful in treatment of the viral disease. More researches have to be done to help and find possible solutions to the various side effects caused by this drug.

REFERENCES

1. Anitha, R. and Ashwini, S. (2017) 'Antihyperglycemic activity of Caralluma fimbriata: An In vitro approach', Pharmacognosy Magazine, p. 499. doi: 10.4103/pm.pm_59_17.
2. Ashwini, S., Ezhilarasan, D. and Anitha, R. (2017) 'Cytotoxic Effect of Caralluma fimbriata Against Human Colon Cancer Cells', Pharmacognosy Journal, pp. 204–207. doi: 10.5530/pj.2017.2.34.
3. Baden, L. R. and Rubin, E. J. (2020) 'Covid-19 — The Search for Effective Therapy', New England Journal of Medicine, pp. 1851–1852. doi: 10.1056/nejme2005477.
4. Bai, Y. et al. (2020) 'Presumed Asymptomatic Carrier Transmission of COVID-19', JAMA, p. 1406. doi: 10.1001/jama.2020.2565.
5. Baron, S. A. et al. (2020) 'Teicoplanin: an alternative drug for the treatment of COVID-19?', International journal of antimicrobial agents, 55(4), p. 105944.
6. Ben-Zvi, I. et al. (2012) 'Hydroxychloroquine: From Malaria to Autoimmunity', Clinical Reviews in Allergy & Immunology, pp. 145–153. doi: 10.1007/s12016-010-8243-x.
7. Chaitanya, N. et al. (2018) 'An insight and update on the analgesic properties of vitamin C', Journal of Pharmacy And Bioallied Sciences, p. 119. doi: 10.4103/jpbs.jpbs_12_18.
8. Chandrasekar, R. et al. (2020) 'Development and validation of a formula for objective assessment of cervical vertebral bone age', Progress in orthodontics, 21(1), p. 38.
9. Chen, Y., Liu, Q. and Guo, D. (2020) 'Emerging coronaviruses: Genome structure, replication, and pathogenesis', Journal of Medical Virology, pp. 418–423. doi: 10.1002/jmv.25681.
10. Clowse, M. E. B. et al. (2006) 'Hydroxychloroquine in lupus pregnancy', Arthritis & Rheumatism, pp. 3640–3647. doi: 10.1002/art.22159.
11. Cunningham, A. C., Goh, H. P. and Koh, D. (2020) 'Treatment of COVID-19: old tricks for new challenges', Critical care / the Society of Critical Care Medicine, 24(1), p. 91.
12. Dave, P. H. and Preetha (2016) 'Pathogenesis and Novel Drug for Treatment of Asthma-A Review', Research Journal of Pharmacy and Technology, p. 1519. doi: 10.5958/0974-360x.2016.00297.3.
13. Deogade, S., Gupta, P. and Ariga, P. (2018) 'Effect of monopoly-coating agent on the surface roughness of a tissue conditioner subjected to cleansing and disinfection: A Contact Profilometric In vitro study', Contemporary Clinical Dentistry, p. 122. doi: 10.4103/ccd.ccd_112_18.
14. Dong, L., Hu, S. and Gao, J. (2020) 'Discovering drugs to treat coronavirus disease 2019 (COVID-19)', Drug discoveries & therapeutics, 14(1), pp. 58–60.

15. Dua, K. et al. (2019) 'The potential of siRNA based drug delivery in respiratory disorders: Recent advances and progress', Drug development research, 80(6), pp. 714–730.
16. Duraisamy, R. et al. (2019) 'Compatibility of Nonoriginal Abutments With Implants: Evaluation of Microgap at the Implant-Abutment Interface, With Original and Nonoriginal Abutments', Implant dentistry, 28(3), pp. 289–295.
17. Ezhilarasan, D., Lakshmi, T., Vijayaragavan, R., et al. (2017) 'Acacia catechu ethanolic bark extract induces apoptosis in human oral squamous carcinoma cells', Journal of Advanced Pharmaceutical Technology & Research, p. 143. doi: 10.4103/japtr.japtr_73_17.
18. Ezhilarasan, D., Lakshmi, T., Nagaich, U., et al. (2017) 'Acacia catechu ethanolic seed extract triggers apoptosis of SCC-25 cells', Pharmacognosy Magazine, p. 405. doi: 10.4103/pm.pm_458_16.
19. Ezhilarasan, D. (2018) 'Oxidative stress is bane in chronic liver diseases: Clinical and experimental perspective', Arab journal of gastroenterology: the official publication of the Pan-Arab Association of Gastroenterology, 19(2), pp. 56–64.
20. Ezhilarasan, D., Apoorva, V. S. and Ashok Vardhan, N. (2019) 'Syzygium cumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells', Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 48(2), pp. 115–121.
21. Ezhilarasan, D., Sokal, E. and Najimi, M. (2018) 'Hepatic fibrosis: It is time to go with hepatic stellate cell-specific therapeutic targets', Hepatobiliary & pancreatic diseases international: HBPD INT, 17(3), pp. 192–197.
22. Ferner, R. E. and Aronson, J. K. (2020) 'Chloroquine and hydroxychloroquine in covid-19', BMJ, p. m1432. doi: 10.1136/bmj.m1432.
23. Fox, R. I. (1993) 'Mechanism of action of hydroxychloroquine as an antirheumatic drug', Seminars in Arthritis and Rheumatism, pp. 82–91. doi: 10.1016/s0049-0172(10)80012-5.
24. G, A. et al. (2017) 'TARGETING THE TARGET USING NANOPARTICLES - A REVIEW', Asian Journal of Pharmaceutical and Clinical Research, p. 6. doi: 10.22159/ajpcr.2017.v10i12.19734.
25. Gheena, S. and Ezhilarasan, D. (2019a) 'Syringic acid triggers reactive oxygen species-mediated cytotoxicity in HepG2 cells', Human & experimental toxicology, 38(6), pp. 694–702.
26. Gheena, S. and Ezhilarasan, D. (2019b) 'Syringic acid triggers reactive oxygen species–mediated cytotoxicity in HepG2 cells', Human & Experimental Toxicology, pp. 694–702. doi: 10.1177/0960327119839173.
27. Gomathi, A. C. et al. (2020) 'Anticancer activity of silver nanoparticles synthesized using aqueous fruit shell extract of Tamarindus indica on MCF-7 human breast cancer cell line', Journal of Drug Delivery Science and Technology, p. 101376. doi: 10.1016/j.jddst.2019.101376.
28. Guan, W.-J. et al. (2020) 'Clinical Characteristics of Coronavirus Disease 2019 in China', New England Journal of Medicine, pp. 1708–1720. doi: 10.1056/nejmoa2002032.
29. Gurunathan, D. and Shanmugaavel, A. K. (2016) 'Dental neglect among children in Chennai', Journal of the Indian Society of Pedodontics and Preventive Dentistry, 34(4), pp. 364–369.
30. Jeevanandan, G. and Govindaraju, L. (2018) 'Clinical comparison of Kedo-S paediatric rotary files vs manual instrumentation for root canal preparation in primary molars: a double blinded randomised clinical trial', European Archives of Paediatric Dentistry, pp. 273–278. doi: 10.1007/s40368-018-0356-6.
31. Jordan, P. et al. (1999) 'Hydroxychloroquine Overdose: Toxicokinetics and Management', Journal of Toxicology: Clinical Toxicology, pp. 861–864. doi: 10.1081/clt-100102466.
32. J, P. C. et al. (2018) 'Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study', Clinical implant dentistry and related research, 20(4), pp. 531–534.
33. Karthiga, P., Rajeshkumar, S. and Annadurai, G. (2018) 'Mechanism of Larvicidal Activity of Antimicrobial Silver Nanoparticles Synthesized Using Garcinia mangostana Bark Extract', Journal of Cluster Science, pp. 1233–1241. doi: 10.1007/s10876-018-1441-z.
34. Lakshmi, T. et al. (2015) 'Azadirachta indica: A herbal panacea in dentistry - An update', Pharmacognosy reviews, 9(17), pp. 41–44.
35. Lipsitch, M., Swerdlow, D. L. and Finelli, L. (2020) 'Defining the Epidemiology of Covid-19 — Studies Needed', New England Journal of Medicine, pp. 1194–1196. doi: 10.1056/nejmp2002125.
36. Liu, J. et al. (2020) 'Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro', Cell Discovery. doi: 10.1038/s41421-020-0156-0.
37. Lover, A. A. (no date) 'Quantifying treatment effects of hydroxychloroquine and azithromycin for COVID-19: a secondary analysis of an open label non-randomized clinical trial (Gautret et al, 2020)'. doi: 10.1101/2020.03.22.20040949.
38. Malli Sureshbabu, N. et al. (2019) 'Concentrated Growth Factors as an Ingenious Biomaterial in Regeneration of Bony Defects after Periapical Surgery: A Report of Two Cases', Case reports in dentistry, 2019, p. 7046203.

39. Mathew, M. G. et al. (2020) 'Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: Randomized controlled trial', Clinical oral investigations, pp. 1–6.
40. Mehta, M. et al. (2019) 'Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases', Chemico-biological interactions, 308, pp. 206–215.
41. Menon, S. et al. (2018) 'Selenium nanoparticles: A potent chemotherapeutic agent and an elucidation of its mechanism', Colloids and Surfaces B: Biointerfaces, pp. 280–292. doi: 10.1016/j.colsurfb.2018.06.006.
42. Molina, J. M. et al. (2020) 'No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection', Médecine et Maladies Infectieuses, p. 384. doi: 10.1016/j.medmal.2020.03.006.
43. Owens, B. (2020) 'Excitement around hydroxychloroquine for treating COVID-19 causes challenges for rheumatology', The Lancet Rheumatology, p. e257. doi: 10.1016/s2665-9913(20)30089-8.
44. Panchal, V., Jeevanandan, G. and Subramanian, E. M. G. (2019) 'Comparison of post-operative pain after root canal instrumentation with hand K-files, H-files and rotary Kedo-S files in primary teeth: a randomised clinical trial', European archives of paediatric dentistry: official journal of the European Academy of Paediatric Dentistry, 20(5), pp. 467–472.
45. Pc, J., Marimuthu, T. and Devadoss, P. (2018) 'Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study', Clinical implant dentistry and related research. Available at: https://europepmc.org/article/med/29624863.
46. Perumalsamy, H. et al. (2018) 'In silico and in vitro analysis of coumarin derivative induced anticancer effects by undergoing intrinsic pathway mediated apoptosis in human stomach cancer', Phytomedicine: international journal of phytotherapy and phytopharmacology, 46, pp. 119–130.
47. Prabakar, J. et al. (2018) 'Comparative Evaluation of Retention, Cariostatic Effect and Discoloration of Conventional and Hydrophilic Sealants - A Single Blinded Randomized Split Mouth Clinical Trial', Contemporary clinical dentistry, 9(Suppl 2), pp. S233–S239.
48. Rainsford, K. D. et al. (2015) 'Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases', Inflammopharmacology, pp. 231–269. doi: 10.1007/s10787-015-0239-y.
49. Rajendran, R. et al. (2019) 'Comparative Evaluation of Remineralizing Potential of a Paste Containing Bioactive Glass and a Topical Cream Containing Casein Phosphopeptide-Amorphous Calcium Phosphate: An in Vitro Study', Pesquisa Brasileira em Odontopediatria e Clínica Integrada, pp. 1–10. doi: 10.4034/pboci.2019.191.61.
50. Rajeshkumar, S., Kumar, S. V., et al. (2018) 'Biosynthesis of zinc oxide nanoparticles usingMangifera indica leaves and evaluation of their antioxidant and cytotoxic properties in lung cancer (A549) cells', Enzyme and microbial technology, 117, pp. 91–95.
51. Rajeshkumar, S., Agarwal, H., et al. (2018) 'Brassica oleracea Mediated Synthesis of Zinc Oxide Nanoparticles and its Antibacterial Activity against Pathogenic Bacteria', Asian Journal of Chemistry, pp. 2711–2715. doi: 10.14233/ajchem.2018.21562.
52. Rajeshkumar, S. et al. (2019) 'Antibacterial and antioxidant potential of biosynthesized copper nanoparticles mediated through Cissus arnotiana plant extract', Journal of photochemistry and photobiology. B, Biology, 197, p. 111531.
53. Ramadurai, N. et al. (2019) 'Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial', Clinical oral investigations, 23(9), pp. 3543–3550.
54. Ramakrishnan, M., Dhanalakshmi, R. and Subramanian, E. M. G. (2019) 'Survival rate of different fixed posterior space maintainers used in Paediatric Dentistry - A systematic review', The Saudi dental journal, 31(2), pp. 165–172.
55. Ramesh, A. et al. (2018) 'Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study', Journal of periodontology, 89(10), pp. 1241–1248.
56. Rathi, S. et al. (2020) 'Hydroxychloroquine prophylaxis for COVID-19 contacts in India', The Lancet Infectious Diseases. doi: 10.1016/s1473-3099(20)30313-3.
57. R, H. et al. (2020) 'CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene', Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, pp. 306–312. doi: 10.1016/j.oooo.2020.06.021.
58. Rome, B. N. and Avorn, J. (2020) 'Drug Evaluation during the Covid-19 Pandemic', New England Journal of Medicine. doi: 10.1056/nejmp2009457.
59. Rothan, H. A. and Byrareddy, S. N. (2020) 'The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak', Journal of Autoimmunity, p. 102433. doi: 10.1016/j.jaut.2020.102433.
60. Sahraei, Z. et al. (2020) 'Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine', International journal of antimicrobial agents, 55(4), p. 105945.
61. Sallard, E. et al. (2020) 'Type 1 interferons as a potential treatment against COVID-19', Antiviral Research,

p. 104791. doi: 10.1016/j.antiviral.2020.104791.
62. Samuel, S. R. (2021) 'Can 5-year-olds sensibly self-report the impact of developmental enamel defects on their quality of life?', International journal of paediatric dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children, 31(2), pp. 285–286.
63. Samuel, S. R., Acharya, S. and Rao, J. C. (2020) 'School Interventions-based Prevention of Early-Childhood Caries among 3-5-year-old children from very low socioeconomic status: Two-year randomized trial', Journal of public health dentistry, 80(1), pp. 51–60.
64. Selvan, S. R. and Ganapathy, D. (2016) 'Efficacy of fifth generation cephalosporins against methicillin-resistant Staphylococcus aureus-A review', Research Journal of Pharmacy and Technology, p. 1815. doi: 10.5958/0974-360x.2016.00369.3.
65. Sharma, P. et al. (2019) 'Emerging trends in the novel drug delivery approaches for the treatment of lung cancer', Chemico-biological interactions, 309, p. 108720.
66. Shen, K. et al. (2020) 'Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement', World Journal of Pediatrics. doi: 10.1007/s12519-020-00343-7.
67. Singh, A. K. et al. (2020) 'Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries', Diabetes & Metabolic Syndrome: Clinical Research & Reviews, pp. 241–246. doi: 10.1016/j.dsx.2020.03.011.
68. Sohrabi, C. et al. (2020) 'Corrigendum to "World Health Organization declares Global Emergency: A review of the 2019 Novel Coronavirus (COVID-19)" [Int. J. Surg. 76 (2020) 71–76]', International Journal of Surgery, p. 217. doi: 10.1016/j.ijsu.2020.03.036.
69. Sridharan, G. et al. (2019) 'Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma', Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 48(4), pp. 299–306.
70. Stein, M., Bell, M. J. and Ang, L. C. (2000) 'Hydroxychloroquine neuromyotoxicity', The Journal of rheumatology, 27(12), pp. 2927–2931.
71. Subashri, A. and Uma Maheshwari, T. N. (2016) 'Knowledge and attitude of oral hygiene practice among dental students', Research Journal of Pharmacy and Technology, p. 1840. doi: 10.5958/0974-360x.2016.00375.9.
72. Subasree, S., Murthykumar, K. and Dhanraj (2016) 'Effect of Aloe Vera in Oral Health-A Review', Research Journal of Pharmacy and Technology, p. 609. doi: 10.5958/0974-360x.2016.00116.5.
73. Tehrani, R. et al. (2008) 'Ocular Toxicity of Hydroxychloroquine', Seminars in Ophthalmology, pp. 201–209. doi: 10.1080/08820530802049962.
74. Touret, F. and de Lamballerie, X. (2020) 'Of chloroquine and COVID-19', Antiviral research, 177, p. 104762.
75. Varghese, S. S., Ramesh, A. and Veeraiyan, D. N. (2019) 'Blended Module-Based Teaching in Biostatistics and Research Methodology: A Retrospective Study with Postgraduate Dental Students', Journal of dental education, 83(4), pp. 445–450.
76. Vijayalakshmi, B. and Ganapathy, D. (2016) 'Medical management of cellulitis', Research Journal of Pharmacy and Technology, p. 2067. doi: 10.5958/0974-360x.2016.00422.4.
77. Vijayashree Priyadharsini, J. (2019) 'In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens', Journal of periodontology, 90(12), pp. 1441–1448.
78. Vijayashree Priyadharsini, J., Smiline Girija, A. S. and Paramasivam, A. (2018) 'In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species', Archives of oral biology, 94, pp. 93–98.
79. Vishnu Prasad, S. et al. (2018) 'Report on oral health status and treatment needs of 5-15 years old children with sensory deficits in Chennai, India', Special care in dentistry: official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry, 38(1), pp. 58–59.
80. Wahab, P. U. A. et al. (2018) 'Scalpel Versus Diathermy in Wound Healing After Mucosal Incisions: A Split-Mouth Study', Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons, 76(6), pp. 1160–1164.
81. Website (no date). Available at: 20. Ren, J. L., Zhang, A. H., & Wang, X. J. (2020). Traditional Chinese medicine for COVID-19 treatment. Pharmacological research, 155, 104743. https://doi.org/10.1016/j.phrs.2020.104743 (Accessed: 1 June 2020).
82. Weiner, A. et al. (1991) 'Hydroxychloroquine Retinopathy', American Journal of Ophthalmology, pp. 528–534. doi: 10.1016/s0002-9394(14)76853-9.
83. Wondafrash, D. Z. et al. (2020) 'Potential Effect of Hydroxychloroquine in Diabetes Mellitus: A Systematic Review on Preclinical and Clinical Trial Studies', Journal of diabetes research, 2020, p. 5214751.

84. Xu, X. et al. (2020) 'Effective treatment of severe COVID-19 patients with tocilizumab', Proceedings of the National Academy of Sciences, pp. 10970–10975. doi: 10.1073/pnas.2005615117.
85. Yazdany, J. and Kim, A. H. J. (2020) 'Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know', Annals of Internal Medicine. doi: 10.7326/m20-1334.
86. Zhou, D., Dai, S.-M. and Tong, Q. (2020) 'COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression', The Journal of antimicrobial chemotherapy. doi: 10.1093/jac/dkaa114.